Vol. XXXVIII December, 1949 No. 12

## SCIENTIFIC EDITION

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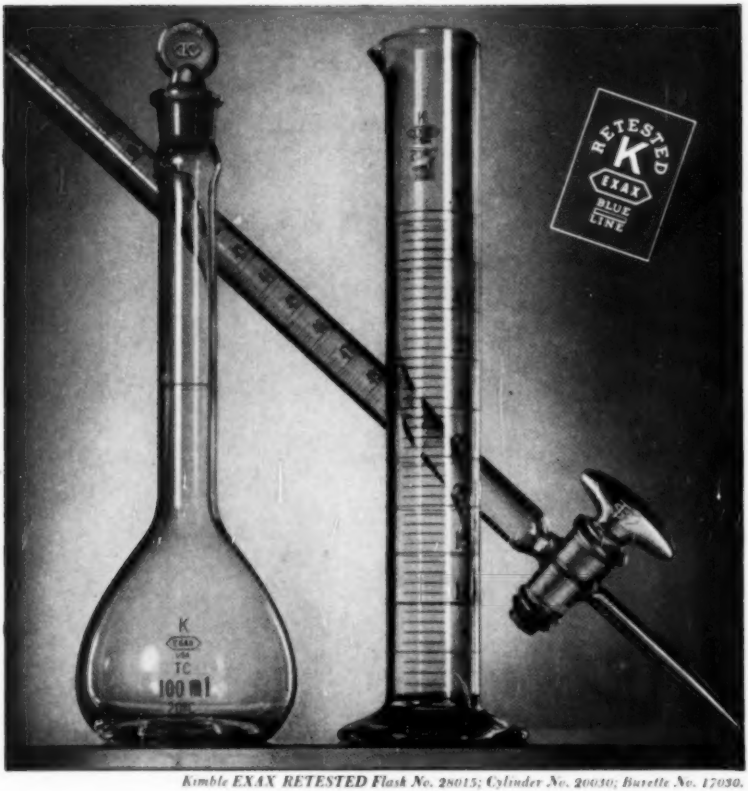


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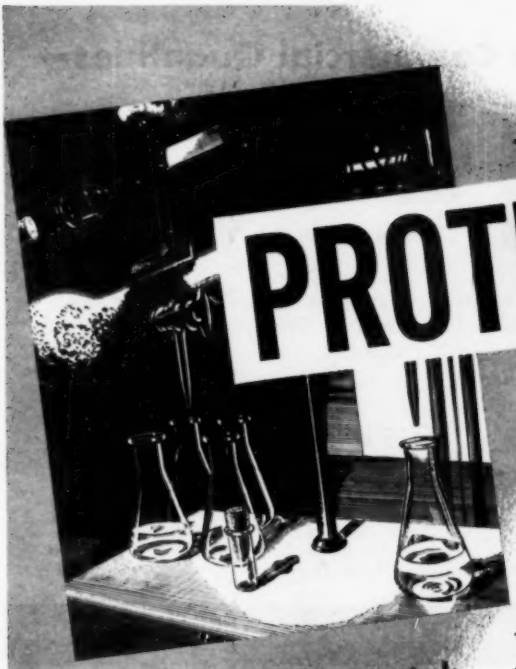

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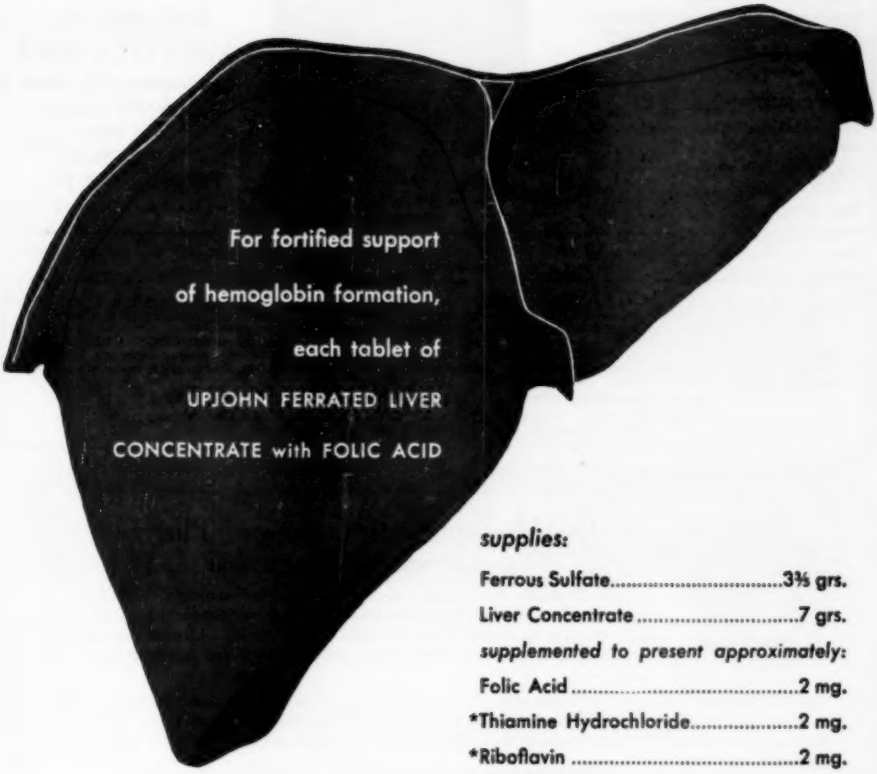


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Entered as second-class matter January 23, 1917, at the Post Office at Easton, Pa., under the act of March 3, 1879, as 24 times a year; Scientific Edition monthly on the fifth; Practical Pharmacy Edition monthly on the 20th. Acceptance for mailing at a special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized July 10, 1918.

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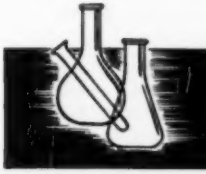

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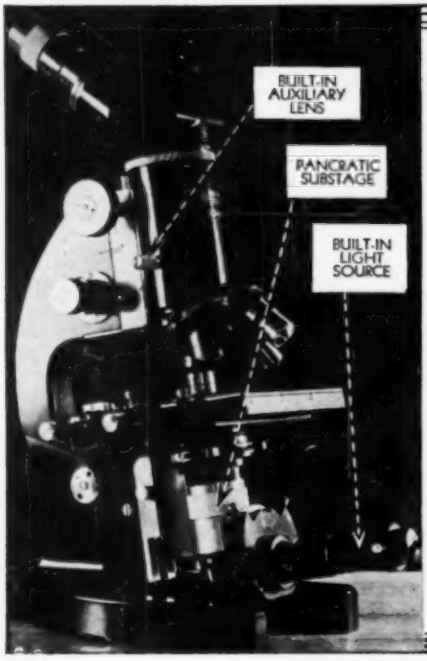


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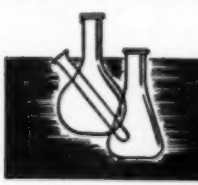

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JUSTIN L. POWERS, EDITOR, WASHINGTON, D. C.

VOLUME XXXVIII | *DECEMBER, 1949* | NUMBER 12 | CONSECUTIVE NO. 24

## Infrared Determination of Aspirin, Phenacetin and Caffeine*

By WILLIAM H. WASHBURN and ELMER O. KRUEGER

**The results of a study on the simultaneous determination of aspirin, phenacetin, and caffeine are reported. A simple chloroform extraction is described, and a method is suggested for the determination of the three-component mixture by means of infrared absorption spectrometry. This procedure was found to be an improvement over previously described methods in that it is less time-consuming and more accurate.**

THE DETERMINATION of a mixture of aspirin, phenacetin, and caffeine in tablets and capsules has always presented a difficult problem. The separation of caffeine from such mixture has provided a major obstacle.

The gravimetric method of the Association of Official Agricultural Chemists (1), which was one of the first attempts on the problem, was found to be open to error and quite time-consuming. The method of Holt (2), based on an ether separation of phenacetin and aspirin from caffeine, while decreasing the time element, was still not as accurate as desired. More recently Green (3) developed a method whereby phenacetin and aspirin are determined directly, and caffeine by difference.

Several attempts were made to develop an ultraviolet method in our laboratories without success. Subsequently, it was attempted to determine the three components simultaneously by means of infrared spectrometry.

### EXPERIMENTAL

**Instrument.**—The instrument used was a Perkin-Elmer Model 12-B, automatic recording spectrometer equipped with a sodium chloride prism, a glass and a lithium fluoride shutter and a slit drive. The slit drive was designed to close the slit continuously as the spectrum is scanned from the longer to the shorter wave lengths, thus giving a more constant energy level and permitting a continuous spectrum. Calibration of wave lengths was determined by use of the spectra of water vapor and of carbon dioxide. Throughout the work, absorption cells were used which are similar to a type designed by Tufts and Kimball (4). The two cells employed were 0.55 mm. thick and the spacers were made of polyethylene. No effort was made to match the cells perfectly, but the difference in optical density between the blank and sample cells at the given wave lengths was determined and checked frequently.

**Infrared Absorption Curves.**—The infrared absorption curves of aspirin, phenacetin, and caffeine in chloroform were recorded from 2.8–14.5 $\mu$, using a 0.55-mm. sodium chloride absorption cell. The spectra were examined for possible analytical bands

* Received July 5, 1949, from the Control Department, Abbott Laboratories, North Chicago, Ill.

for each component. As can be seen from the curves in Fig. 1, aspirin has a strong band at 9.27 μ, phenacetin at 8.99 μ, and caffeine at 10.26 μ. These were chosen as the analytical peaks for this determination. At each of these bands there is a minimum of absorption due to the other two components.

**Working Curves.**—From preliminary experimentation, it was found that the most suitable concentration that could be obtained for aspirin was in the range 10–12 mg./cc. of chloroform, for phenacetin in the range 7–8 mg./cc. and for caffeine 1.5–2.0 mg./cc. This is due to the fact that the usual proportions of the mixture are in the ratio of approximately: 11.5 parts of aspirin, 8.0 parts of phenacetin, and 1.6 parts of caffeine. Therefore, concentrations were chosen whereby caffeine, being in the smallest amount, was given as high a concentration as possible without obtaining a concentration of aspirin past the point of sensitive detection.

Concentrations of aspirin in the range 6–12 mg./cc. of chloroform were prepared and, using chloroform as a blank, spot readings were taken at 9.27 μ, 8.99 μ, and 10.26 μ employing the technique of L. W. Daasch (5). Concentrations of phenacetin in the range 5–10 mg./cc. and caffeine in the range 1–2 mg./cc. were prepared, and in a similar manner optical densities were noted at the same wave lengths. Optical densities were then plotted against concentrations for each of the three components at 9.27 μ, 8.99 μ, and 10.26 μ. As can be seen in Fig. 2, the relationship was found to be linear.

**Method.**—Weigh 20 tablets accurately and grind to a fine powder in a mortar. Weigh accurately an aliquot equivalent to 1 tablet and transfer quantitatively to a 250-cc. separatory funnel. Suspend the powder in 50 cc. distilled water and extract with 6 portions chloroform A. R. (25, 20, 20, 20, 15, 15 cc.). Filter the chloroform extracts through a pledget of cotton previously saturated with chloroform into a suitable flask.

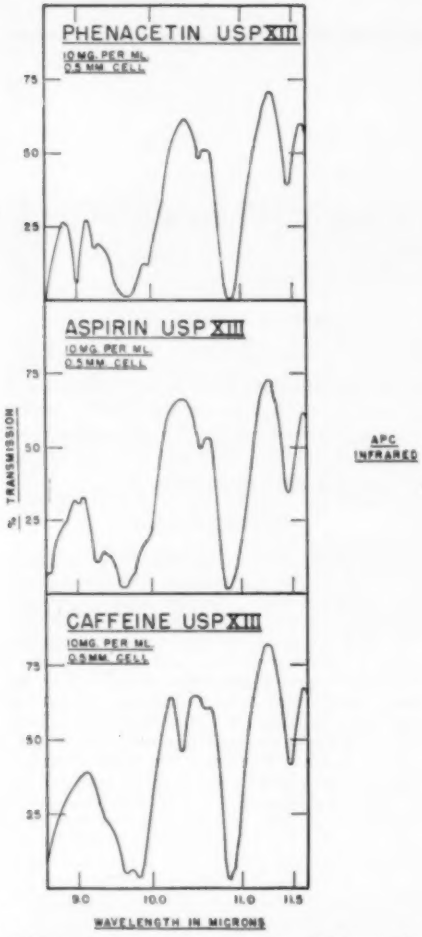


Fig. 1.—The absorption spectra of phenacetin, aspirin and caffeine in chloroform solution. (The strong bands at 9.7, 10.85 and 11.5μ are due to chloroform.)

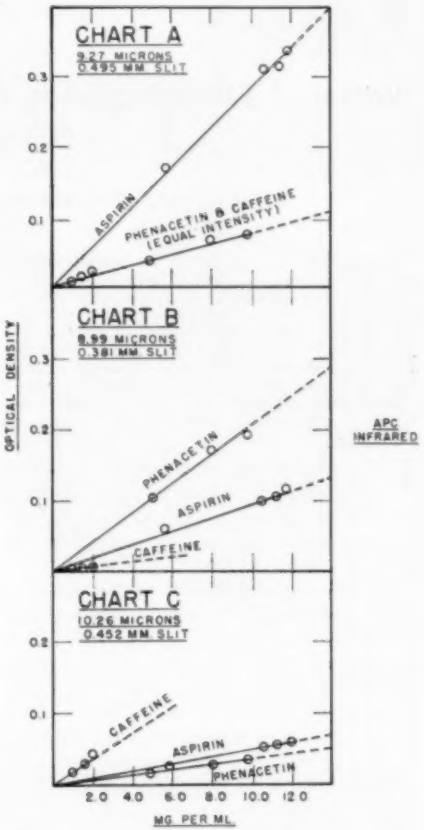


Fig. 2.—Plot of optical density against concentration for aspirin, phenacetin and caffeine in chloroform solution at 9.27, 8.99, and 10.26μ.

Evaporate to dryness on a steam bath with the aid of a stream of nitrogen. Dry for two hours in a vacuum desiccator, or until residue is completely crystalline. Dissolve in exactly 20 cc. of chloroform. Fill the blank cell with chloroform, and adjust the slit for full-scale deflection at 9.27 $\mu$. Fill the sample cell with solution prepared above and observe the optical density. Repeat this procedure at 8.99 $\mu$ and at 10.26 $\mu$.

aspirin at 10.26 $\mu$ from the aspirin-working curve in Chart C, and using the corrected concentration of phenacetin, determine the optical density due to phenacetin at 10.26 $\mu$. Subtract the sum of these optical densities from the optical density of the sample solution at 10.26 $\mu$. From this corrected optical density determine the corrected concentration of caffeine from the caffeine-working curve in Chart C.

TABLE I.—RESULTS OF ANALYSES BY THE PROPOSED METHOD

| | Sample No. | Aspirin, Mg./Cc. Theory | Aspirin, Mg./Cc. Recovered | Phenacetin, Mg./Cc. Theory | Phenacetin, Mg./Cc. Recovered | Caffeine, Mg./Cc. Theory | Caffeine, Mg./Cc. Recovered |
|---|---|---|---|---|---|---|---|
| Laboratory preparation | 1 | 11.36 | 11.22 | 8.18 | 8.00 | 1.62 | 1.63 |
| | 2 | 11.44 | 11.30 | 8.10 | 8.00 | 1.62 | 1.65 |
| Commercial tablets | 1 | 11.34 | 10.90 | 8.10 | 8.20 | 1.62 | 1.60 |
| | 2 | 11.34 | 11.10 | 8.10 | 8.22 | 1.62 | 1.56 |
| | 3 | 11.34 | 11.00 | 8.10 | 8.20 | 1.62 | 1.60 |
| Commercial capsules | 1 | 11.34 | 11.30 | 8.10 | 8.10 | 1.62 | 1.65 |
| | 2 | 11.34 | 11.00 | 8.10 | 7.90 | 1.62 | 1.70 |

## GRAPHICAL METHOD OF COMPUTATION

**First Approximation.**—From the optical density of the sample solution obtained at 9.27 $\mu$, determine the concentration of aspirin from the aspirin-working curve in Chart A. Using the same procedure, determine the approximate phenacetin concentration from the optical density of the sample solution obtained at 8.99 $\mu$ and the phenacetin-working curve in Chart B, and determine the approximate concentration of caffeine from the optical density at 10.26 $\mu$ and the caffeine-working curve in Chart C. These approximate concentrations will all be too high because at each of these wave lengths the absorption obtained is due to all three components.

**Second Approximation.**—Using the concentration of phenacetin obtained in the first approximation, determine the optical density due to phenacetin at 9.27 $\mu$ from the phenacetin-working curve in Chart A and using the concentration of caffeine obtained in the first approximation determine the optical density due to caffeine at 9.27 $\mu$ from the caffeine-working curve in Chart A. Subtract the sum of these optical densities from the optical density of the sample solution at 9.27 $\mu$. Using this corrected optical density, determine the corrected concentration of aspirin from the aspirin-working curve in Chart A. Using the corrected concentration of aspirin, determine the optical density due to aspirin at 8.99 $\mu$ from the aspirin-working curve in Chart B, and using the concentration of caffeine obtained in the first approximation, determine the optical density due to caffeine at 8.99 $\mu$ from the caffeine-working curve in Chart B. Subtract the sum of these optical densities from the optical density of the sample solution at 8.99 $\mu$. From this corrected optical density, determine the corrected concentration of phenacetin from the phenacetin-working curve in Chart B. Using the corrected concentration of aspirin, determine the optical density due to

Using the corrected concentrations, repeat the calculation as directed in the second approximation above. Repeat this process until subsequent approximations make negligible change in the concentration of each component. A complete computation requires about five minutes. If preferred, the computation may be determined algebraically by solving for three unknowns.

**Results.**—In Table I are listed a series of determinations on known mixtures and commercial preparations of aspirin, phenacetin, and caffeine. The values were reproducible within approximately $\pm 2\%$.

## SUMMARY AND CONCLUSIONS

1. An infrared method has been developed for the simultaneous determination of aspirin, phenacetin, and caffeine in mixture.
2. This determination consists of a simple chloroform extraction, and does not involve the tedious task of separating the components.
3. The manipulations are simple and rapid to perform. A determination can be completed within four hours.
4. Reproducibility is in range $\pm 2\%$.
5. The method is specific in that a complete infrared curve may be scanned and the presence of each component confirmed.

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# The Metabolism of Iodine Compounds*,†

By WILLIAM T. SALTER, GOPAL KARANDIKAR‡ and PAUL BLOCK§

THE nonmetallic element iodine belongs to the so-called group of "halogens," of which chlorine, bromine, and fluorine are the other outstanding members. In its solid form iodine occurs as heavy shining crystalline scales, which are blackish gray in color. When heated, however, these sublime to yield a beautiful reddish violet vapor. Even the solid scales or the alcoholic tinctures have a pungent acrid odor which is characteristic. The atomic weight of iodine is 126.9, and its molecular weight twice this value. Its atomic number is 53. It occurs only in traces in most natural substances, but is especially concentrated in sea water and certain mineral waters, in marine plants and corals, and in sea food such as oysters. Its salts are commonly found in cough medicines. It was discovered in 1811 by Courtois in France. It can be prepared from the ashes of kelp (i.e., seaweeds) or from crude Chile saltpeter. In its elementary form it colors starch or starched objects a deep blue. Recently, under the auspices of the Atomic Energy Commission, a copious supply of radioactive iodine has become available. In the process of physical decay, for example, each atom of the eight-day isotope,[1] $I^{131}$, yields both beta and gamma radiations.

## THE DISCOVERY OF IODINE

If one considers how iodine happened to be discovered, it seems that two major situations lie back of this important finding. The first of these was contemporary, namely, the ambition of Napoleon Bonaparte and his need for gunpowder. The second of these was more fundamental, namely, Nature's discovery, millions of years ago, that iodine and bromine (both halogens) would form organic compounds which were useful in the constitution and function of primitive organisms. About 1811 these two circumstances came into conjunction and the result was the discovery of a new element.

By 1810 the continued drain of Napoleon's campaigns upon the natural resources of France, together with the limitation of sources of niter (saltpeter) from other parts of the world because of the blockade, led to a concerted effort in France for the exploitation and development of new sources of nitrate. Temporarily a profession of salpêtriers had sprung up, devoted to the production of nitrate from organic materials. Originally potash was used as a source of the potassium but as wood became scarce other materials were tried. Furthermore, the production of ammonia and nitric acid from decaying vegetable and animal sources became an increasing problem. Consequently, certain of the salpêtrières turned to seaweed as a raw material, and particularly to the variety known as "le varech." The story of the corrosion of his copper-lined vats by Monsieur Courtois (1), (published in 1812), followed by the observation that the distillate from sulfuric acid yielded violet-colored fumes, is familiar to all of you, I am sure. The finding was checked and corroborated by the eminent French chemist Gay-Lussac (2), who named this purplish element "violet" in Greek, after the humble but beautiful flower, *'Ιον*, to which it was likened—i.e., *'Ιο-ειδής* or *'Ιώδης*.

For thousands of eons Nature had been utilizing this element in the construction of primitive organisms. Possibly the high prevalence of iodine in sea water relative to the waters of the land had something to do with this. At any rate, together with bromine, iodine is a prominent constituent of the sea fans, corals, and sponges. In particular, the species *Gorgonia* is replete with iodine. In general, many marine plants contain more iodine than does terrestrial vegetation and among these are the large brown forms called kelp and various other seaweeds. The same holds true of the ash of these plants, when burned. Thus it came about that when Courtois' factory (salpêtrière) turned to "le varech" as a starting material in the manufacture of niter he unwittingly brought this unknown element into the picture.

Because of man's greater interest in mammalian physiology than in plant physiology, we know today much more about the behavior and function of iodine in mammalian organisms than in the corals. Among others, Professor Werner Bergmann (3), of Yale in recent years has studied the participation of organically bound iodine and bromine in the structure of sea organisms. This interest is a traditional one at Yale because Wheeler and Jamieson (4) as early as 1905 synthesized iodo-gorgonic acid, previously isolated by Drechsel (5) from certain marine forms (*Gorgonia*) and identified it as diiodotyrosine.[2] In 1895 Baumann (6) had discovered the presence of iodine in the human thyroid

* Received June 24, 1949, from the Laboratories of Pharmacology and Toxicology, Yale University School of Medicine, New Haven, Conn.

Presented to the Scientific Section of the A. PH. A., Jacksonville meeting, April, 1949, by Dr. William T. Salter, recipient of the first (1948) Iodine Educational Bureau Award for outstanding research in the chemistry and pharmacology of iodine.

† This work was supported by grants from the Committee on Research in Endocrinology, National Research Council, the Connecticut Cancer Society and the Fluid Research Fund of Yale University School of Medicine.

The authors wish to thank Miss Elizabeth Runels for her technical assistance and Mrs. Katherine H. Barhydt for the preparation of the manuscript.

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[1] $I^{131}$, the radioactive iodine used in these investigations, was obtained from the Oak Ridge National Laboratory, Carbide and Carbon Chemicals Corp., Oak Ridge, Tenn., through the Isotopes Division, Atomic Energy Commission.

[2] For the diiodotyrosine and "Priodax" used in these studies the authors are indebted to Dr. Edward L. Henderson of Schering Corp. For the thiouracil used they wish to thank Dr. R. P. Parker of the Calco Chemical Division of American Cyanamid Co.

and shortly thereafter had assumed that diiodotyrosine was present. Subsequently Oswald (7) tried for many years to isolate it from mammalian thyroid tissue. The actual identification was not made until 1930 by Harington and Randall (8), but at that late date the isolation was merely a necessary confirmation of what seemed to most investigators to be a foregone conclusion. Of course, the inquisitive scientist, on learning these facts, will at once begin to wonder how iodine in sea water can be built into an organic compound within organisms, and what role organically bound iodine plays in the metabolism both of plants and of animals. From the standpoint of the pharmaceutical chemist and the pharmacologist these findings are of basic interest, because a knowledge of the biochemistry of natural iodine compounds inevitably will pave the way for the development of useful synthetic products.

## THREE CHIEF CATEGORIES OF IODINE IN METABOLITES AND DRUGS

For purposes of classification and for convenience in cataloguing the main facts about iodine metabolism in relation to drugs, it is useful to divide these materials into three chief groups. These are as follows:

**Iodine in a High State of Potential Biochemical Activity**—This class would include chiefly elementary iodine itself, and solutions and tinctures of elementary iodine. It would also include some of the complexes or compounds of iodine, such as that produced with glycine, nitrogen tri-iodide or the starch-iodide complex, in which a peculiar type of chemistry governs the behavior of each compound.

**The Iodide Ion in Various Media.**—From the physiological point of view, iodide itself is the starting point of nearly all natural events. The ion exists free in sea water and in the blood stream of man. When iodine-containing medication is administered to animals or to man, ordinarily a large part of the iodine in organic compounds ends up as iodide, even though it was organically bound at the start. When sea water or natural body fluids are evaporated, the great preponderance of sodium leads to the isolation of the iodide largely in the form of sodium iodide. However, in the organism, the alkali salts of hydriodic acid are carried largely in dissociated form. Therefore, we need not concern ourselves with physiological distinctions between potassium and sodium iodide under ordinary circumstances.

**Organically Bound Iodine.**—In addition to those compounds containing iodine which exist in natural sources, there is now a host of iodine-containing compounds which have been used for physiological investigation or for therapeutic purposes. A few of these are of natural origin and their properties are part and parcel of the biochemistry of life. Thyroxine and thyroglobulin are instances of this type. A large number of compounds are known, however, which are man-made and are utilized for specific purposes. This phase of pharmaceutical chemistry is only in its infancy. Indeed, the properties of these compounds are so manifold and interesting that doubtless much more work will be done in the development of interrelated and extrapolated chemical formulas in the future.

### Iodine in a State of High Potential Activity

At the moment the chief pharmacological interest in elementary iodine, which to the biologist appears to represent a high state of potential biological activity, is based upon its ability to combine with protein. Its combination with the constituent amino acids of protein probably involves chiefly three types of reaction. The first is the iodination of tyrosine which has been studied by Harington (9). The second, studied by Johnson and Tewkesbury (10), is the production of thyroxine. This process goes on even though the tyrosine is bound into the peptide chain of the proteins, as demonstrated by the studies of Muus, Coons, and Salter (11), and of Turner, Williamson, and Reineke (12). This combination of elementary iodine with protein has been applied in three general ways. First, active substitutes for thyroid medication have been produced, which will relieve the human disease known as myxedema. Such material has been tested in milch cows for its ability to increase milk production, and in hens to increase egg production. Secondly, the reaction has been employed in scientific studies to label foodstuffs and antibodies, much as fat was formerly distinguished by its iodine content in feeding experiments. Finally, the combination with protein has been applied widely for its effect on bacteria and parasites.

Apparently when this reaction occurs, many bacterial and mammalian proteins or enzyme systems are no longer able to function naturally within the cell protoplasm. Probably frank coagulation of the protein does not necessarily occur until a further reaction supervenes, namely, the iodination of histidine as described by Li (13), and by Blum and Grützner (14). By this time, drastic oxidative processes have also occurred; leading, first, to the formation of thyroxine or close derivatives thereof (15, 16) and, secondly, to the splitting off of sulfur from the cysteine and methionine components, so that the protein becomes obviously denatured. Once this action, which is truly violent in a biological sense, has occurred, the subsequent fate of the iodine is the fate of the individual iodinated components of the protein.

Although elementary iodine has enjoyed an extensive vogue as a bactericide, obviously its use will be limited by the fact that it does not distinguish between bacterial and mammalian protein. In a sense, therefore, it may be regarded as a chemical cauterant which simply coagulates all living material within its sphere. The end products of its action must be broken down and dissolved or sloughed off. Consequently, the deep ulcers formed after the injudicious use of elementary iodine delay healing, because often the wound must heal by granulation and the formation of scar tissue. To avoid this mishap, in recent years attempts have been made to moderate and control the action of the element—either by the adjustment of the ointment base in which the iodine is suspended or by the formation of iodine-buffer systems, notably with glycine. The actual chemistry involved in this reaction is still not very clear, but it rather resembles the oxygenation of hemoglobin, in that such glycine-buffer complexes slowly and reversibly yield elementary iodine which becomes available as each preceding moiety is utilized. This feature is

certainly a characteristic buffer action. Moreover, more dilute tinctures of iodine have become standard, in order to assure a milder action. Besides, the routine surgical practice of washing off the excess with alcohol is being learned by millions of anxious mothers.

When such mild complexes or dilute solutions of elementary iodine are ingested, they combine rapidly with the food or with the mucus and epithelial lining of the alimentary canal to form iodinated protein *in situ*. If the latter combination is particularly extensive, of course irritation of the gut occurs, which is identified by nausea and vomiting or even by bloody diarrhea. Ordinarily, however, such situations occur only after suicidal attempts or accidents.

The laity is apt to attach too much importance to this corrosive effect without due recognition of the concentration involved. For example, one or two drops of tincture of iodine in a glass of water are tolerated easily by people undergoing treatment for goiter of various types, particularly if the iodine-containing water is sipped during meals. Furthermore, the use of iodate, $IO_3^-$, in the making of bread has created undue alarm. In the ordinary processes in which iodate has been used for bread making, a very small concentration is mixed with a huge excess of vegetable protein and milk. Long before the doughy mass is ready for the oven, this iodine-containing oxidizing agent will have been reduced and combined to a large extent with the vegetable and animal proteins. That portion which escapes combination with the protein, of course, will persist as iodide. If any trace fails to react within the first few minutes, it will surely be decomposed under the conditions of baking. Failure to appreciate the instability of the higher oxidation forms of iodine in the presence of organic matter has led to a great deal of useless apprehension and unfounded fear. Many years ago Cohn (17) and others (18) even administered dilute solutions of potassium iodate in water directly to dogs, and found that the resulting metabolic story was primarily that of simple sodium iodide in equivalent concentrations.

### Iodine and Skin

It is often forgotten that elementary iodine penetrates the skin and is absorbed into the circulation. Probably the oily sebaceous glands and the sweat glands facilitate this assimilation. Most of the absorbed material is converted into iodide and enters the blood stream, to be distributed to all parts of the body. In former times, goiters used to be treated by local applications of tincture of iodine or of milder iodine-containing ointments to the neck. There is no question that the therapy was successful. The amusing fact, however, is that the assimilated iodine first had to be carried by the blood to the lungs and the heart; and then pumped back through arteries to the thyroid gland before it could relieve the thyroid swelling. Indeed, even the pituitary gland within the skull was involved in the disease and its relief.

### The Pharmacology of Iodide

From the physiological point of view, iodine metabolism in the normal man starts with the inorganic form, iodide. The same, of course, is true of the corals and sea fans. In the tissue juice of these sea organisms free iodide ion circulates by diffusion, whereas in the blood of man it is pumped about in the circulation of the blood. In both cases, however, as shown by the fact that it is uniformly distributed throughout the interstitial fluid, and with minor exceptions and reservations, it probably also permeates uniformly the water in the cell sap. Studies by Wallace and Brodie (19) have shown that at concentrations which are well above physiological levels this picture also holds.

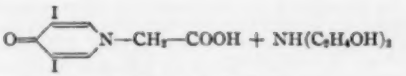
Of course, the old observation of Pliny (20), "Tales sunt aquae quales terrae per quas fluunt," is true in the case of men and dogs or other domestic beasts. Dr. David Marine, an eminent pioneer in the study of thyroid disease, was once late for his lecture in the Middle West because he stopped to examine the goiters of three dogs he met. In the backwoods of Michigan or even in the Connecticut valley, the iodide circulating in the blood is almost at the vanishing point, namely, at about half a microgram per cent. On the other hand, the good Catholics in Boston, Mass., who live close to the sea and who eat fish twice a week—not to mention the excellent oysters to be obtained in the heart of that city—carry in their blood streams a higher concentration of iodide in evidence of their piety, namely, possibly two or three micrograms per cent. At the other extreme, the victim of tertiary syphilis a generation ago who was treated rigorously with potassium iodide by his physician, might have a plasma concentration of several hundred micrograms per cent.

In my monograph (21) I have delineated four arbitrary but useful levels of iodine intake. These are: (*a*) the natural level of iodine intake; (*b*) the prophylactic level against simple goiter; (*c*) the therapeutic level (against exophthalmic goiter with hyperthyroidism); and (*d*) the fibrolytic level. In the last category are included various treatments which the older clinicians have used and which were denounced as leading to "iodine debauchery" by Veil and Sturm (22). Indeed some of the victims of this heroic sort of therapy showed extreme emaciation, not to mention the coryza, general catarrh, and pustular acne characteristic of iodism. Before better therapy became available, however, many a syphilitic patient saw his gumma melt away and many a farmer's actinomycotic jaw was relieved by such therapy. It has achieved its bad name because, as they used to say in Germany, "Wenn man weiss nicht wie so, warum . . . Dann gibt man jod kalium." In other words, when you don't know what else to do, give the poor patient some potassium iodide.

Obviously, whenever iodine in the first category (that of high oxidation) is administered, one is also administering iodide ions indirectly, because such compounds rapidly break down to form the inorganic form, i.e. iodide. This is true even when cutaneous ointments are given or when tincture of iodine is painted on the skin. Indeed even the carrying about of little amulets containing elementary iodine, so common in the French Midi a century ago, can lead ultimately to a very definite absorption of iodine or of iodide through the oily sebaceous glands, and goiter may actually be prevented by such superstition. Its abuse, however, led to legislation in the French Midi against its general use without proper medical supervision.

### Organic Compounds of Iodine

Finally, there are a number of compounds of miscellaneous character in which the halogen is incorporated into an organic radical with the purpose of influencing its properties and pharmacological utility. The number of such compounds is growing and obviously we cannot hope to mention them all today. In our time, they have perhaps been brought to greatest recognition through the researches of Evarts Graham (23), and his colleagues (24), who developed a group of compounds which were radiopaque. For example, tetraiodophenolphthalein derivatives were found to be concentrated by the liver, excreted through the biliary tract, and ultimately concentrated in the gall bladder. The four iodine atoms in the molecule rendered solutions of this substance dense enough to cast a differential shadow when illuminated by X-rays. Consequently, it was possible to visualize the gall bladder and to detect cholesterol stones by virtue of their lighter density. In similar fashion Homer Smith (25) and his colleagues have used other iodo-compounds (Table I) to study renal clearance. A number of these have been widely used under the names of "Uroselectan," "Skiodan," "Diodrast," and several other proprietary names. Combined with creatinine—or, better, xylose—clearances, these substances are useful in measuring the mass and function of the tubules of the kidney, and have contributed considerably to our understanding of renal function and the fundamental background of Bright's disease. In addition to their use by intravenous injection, such compounds may be employed in local instillations. An example is Iodopyracet, U. S. P. (I), i.e., "Diodrast," which can be used to visualize the pelvis of the kidney, the bladder, and other urinary passages. A sterile aqueous solution of the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid is made at about 35% concentration. Because the dry salt contains about 62% of the dense element iodine in combination, as shown in formula I, it casts a definite shadow in the X-ray picture.



Iodopyracet, U. S. P.

(I)

Several such compounds are now available. Among these are Methiodal Sodium with about 52% iodine; Neo-Iopax also with 52%; Hippuran with approximately 36%; and Iodoalphonic Acid with about 51% iodine. In modern times this genito-urinary application has become relatively more important than the original gall bladder test of Graham. Both procedures, however, illustrate the fundamental feature of differential concentration and excretion at certain sites in the body. In both cases, also, it is the density of the inherent iodine atoms which renders the substances useful.

In other situations, the halogen has been introduced into the molecule for the purpose of influencing its over-all properties, both chemical and biological. It will be recalled that some of our best antimalarial drugs and antibiotics contain chlorine in organic combination. It used to be thought that these substituted halogen atoms exerted their influence by yielding free chlorine within the cell protoplasm. Indeed, the same theory was held until within a decade for the action of mustard gas as used in gas warfare. It would now appear that this theory is too naive and that the role of the chlorine in the organic molecule is much more subtle. The same may be said of many organic compounds of iodine. It is true, of course, that certain compounds like iodoform do yield a certain amount of iodide within the body and probably also (in the presence of protoplasmic oxidase systems) a trace of iodine or hypoiodous acid as a consequence of their degradation. In general, however, this would seem to be a minor and probably incidental feature of their metabolism within the mammalian organism.

TABLE I.—ORGANIC IODINE COMPOUNDS IN RENAL CLEARANCE

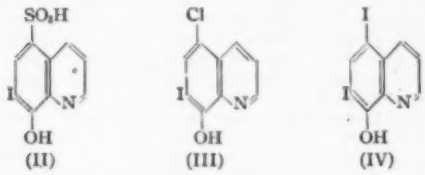
[From Smith, H. W., and Ranges, H. A., (25)]

| Type of Compound | | Average Inulin Clearance Ratio | Tm[a] mM. per Minute | Per cent Free[b] | Approximate Per Cent Depression Effected by 1.0 mM. per Liter in Plasma — On Self-clearance | Approximate Per Cent Depression Effected by 1.0 mM. per Liter in Plasma — On Simultaneous Phenol Red Clearance |
|---|---|---|---|---|---|---|
| Diodrast..... | 3,5-Diiodo-4-pyridone-N-acetic acid | 6.0 | 0.3 | 72 | 50 | 85 |
| Hippuran ..... | Sodium ortho-iodohippurate | 5.4 | 0.6 | 30 | 25 | 80 |
| Iopax..... | Sodium 2-oxo-5-iodopyridine-N-acetate | 5.0 | 0.2 | 56 | 65 | 75 |
| Neoiopax..... | Disodium N-methyl-3:5-diiodo-4-pyridoxyl-2:6-dicarboxylate | 1.2 | 0.01 | 74 | 25 | 55 |
| Skiodan..... | Sodium mono-iodomethane sulfonate | 1.2 | >0.1 | 82 | *5 | *5 |

[a] The maximal rate of tubular excretion. The data on diodrast and hippuran are quoted from Smith, Goldring, and Chasis, *J. Clin. Investigation*, **17**, 263(1938).

[b] Per cent of total dye filterable at a total concentration of 1.0 mg. per cent, in human plasma containing 4 per cent albumin.

As examples of this total-molecule effect certain drugs used against the organisms of amebic dysentery may be cited. These include Chiniofon, U. S. P. (7-iodo-8-hydroxy-quinoline-5-sulfonic acid) (II); Vioform, N. N. R. (5-chloro-7-iodo-8-hydroxy quinoline) (III); and Diodoquin (5,7-diiodo--8-hydroxy quinoline) (IV). Their respective chemical formulas appear below:




(II) (III) (IV)

The compound last named is much less toxic than Vioform, which contains one chlorine atom instead of an iodine. The danger of gastrointestinal irritation and of liver damage is definitely less. Nevertheless (when combined with emetine from ipecac) it has produced very satisfactory therapeutic results (26). Obviously, in this instance, the important iodine atom has merged its identity with that of the whole molecule, and one cannot claim that this effect is due only to elementary iodine.

Of course there are compounds which are effective on topical administration because they slowly evolve elementary iodine locally. Thymol iodide, the dusting powder known as "Aristol," is one of these. On the other hand, the local effect of Vioform in treating infection with *Trichomonas vaginalis* may well be unrelated to free iodine. It is interesting that the official Iodine Tincture of U. S. P. XIII, once known as "mild surgical tincture of iodine," contains only 2% of free iodine. The "strong iodine tincture" of N. F. VIII is much more likely to produce irritation and blistering of the skin because it contains 7% of free iodine. This difficulty could usually be avoided if the excess of iodine were always washed away with 70% alcohol after a minute or two of action. Modern ointment bases act somewhat similarly by withholding the elementary iodine from the skin or ulcer, at least temporarily, or by paying it in slowly.

## DEGRADATION TO IODIDE

Most of the compounds now available in all three of the categories just surveyed begin to decompose into iodide soon after they are admitted into the mammalian body. This feature holds even when they are still in the alimentary canal and not strictly *within* the organism proper. How this degradation occurs is a matter of some interest, because the persistence of action of drugs containing iodine (and in which the iodine atom is an essential component) depends in part upon the rate of decomposition. Many pharmaceutical chemists and pharmacologists do not appreciate the fact that whenever an iodine-containing organic chemical is administered for therapeutic or diagnostic purposes, iodide is simultaneously being administered in potential form. This is true not only for substances such as sodium iodate (*in*organic in nature) but also for volatile organic compounds like ethyl iodide which is sometimes used for the determination of the circulation rate. It is also true of thyroglobulin and iodocasein, and for such classical compounds as iodoform. All of these substances begin to release iodide soon after their injection or ingestion into the animal organism, or even on contact with raw flesh. This decomposition may occur through bacterial action or by simple hydrolysis within the alimentary canal. A good deal of decomposition of ingested material occurs, however, in the liver after absorption. Undoubtedly once a steady state of metabolism has been established, the iodine-containing compounds are degraded by the tissues at large, including the blood.

**Iodases.**—Every now and then some investigator revives the problem of iodases—namely, enzymes specifically concerned with the fixation of iodine in organic molecules and, conversely, with the removal of iodine therefrom. Years ago, Blum (27) pointed out that such catalysts must exist in the blood stream. Recently, Curtis and his colleagues (28) have shown that when iodide is added to blood plasma, after a time the iodide is incorporated into the plasma protein by some sort of linkage not yet understood. This combination does not occur if the blood is heated or treated with a protein-coagulant like alcohol or acetone. Of course it is known that compounds like thyroxine are readily decomposed by hydrogen peroxide and by catalysts such as spongy platinum or palladium saturated with hydrogen. Therefore it is conceivable that some decomposition of iodo-compounds occurs as a non-specific effect of reducing agents or of oxidation-reduction systems such as peroxidases. Obviously this subject needs much more study.

An interesting beginning has been made by Keston (29), who showed that the xanthine oxidase of milk could convert iodide into diiodotyrosine and from this small amounts of thyroxine were formed. The effect of thiouracil and related goitrogens in the thyroid gland strongly suggests that specific enzyme systems exist which build iodine into diiodotyrosine and then into thyroxine. Indeed by the use of successive goitrogens like thiocyanate and thiouracil it is possible to present evidence, as I have done (30), that the iodide ion is first trapped by an iodinase system, which is then acted upon by a peri-odase system to form diiodotyrosine. Of course this *schema* as shown in Fig. 6, is quite analogous to the iodase systems which are classically known to guide cellular oxidation. In the latter example, however, atmospheric oxygen is first trapped by an oxygenase and the resulting complex is then acted upon by a peroxidase to liberate the equivalent of nascent oxygen.

Inasmuch as enzyme systems act in either direction according to thermodynamic conditions, it is not necessary to assume that specific biological systems exist both for the building up and for the breaking down of organic combinations of iodine. Nevertheless it is quite possible that in the tissues no such highly developed iodinase system exists as in the thyroid gland. Indeed it is even conceivable that the enzymes or enzymic systems which break down thyroxine and other iodo-compounds in cells are no different than those which decompose various metabolites which do not contain iodine. Ultimately a careful study of these enzyme systems in tissues must be made from the standpoint of the persistence

of iodine-containing drugs within the body. Such knowledge will doubtless lead to the development of more stable drugs, the composition of which will continue unaltered in the body for longer periods than now encountered.

## THE FATE OF IODIDE

**The Thyroid Route.**—When iodide is admitted into the body, it is distributed rapidly through all body fluids. It is probably absorbed even through the stomach wall. When administered through a stomach tube or through a duodenal catheter, it appears in the blood stream within five to ten minutes and even in the saliva within about fifteen minutes. If the alimentary canal is empty, most of the iodide is absorbed within an hour. If food is present, absorption is slower because some of the dissolved iodide is retained in the chyme. Once the iodide ion is admitted to the circulation, it is distributed rapidly throughout all body water. Normally the concentration is of the order of one microgram per cent, but when medication high in iodine is administered, the concentration in body fluids may mount to one or more *milligrams* per cent, i.e., over a thousand times the usual value. Within an hour or two it will come into equilibrium with the spinal fluid and soon the concentration in that liquid will be the same as in the plasma water. This does not mean that the *total* concentration of iodine in spinal fluid is equal to that of plasma. Actually, spinal fluid contains only about one-fifth of the total iodine of the human plasma, because most of the iodine normally in human plasma is *organically* fixed. So uniform is this distribution of iodide in body fluids that radioactive tracer iodide has been used to measure the volume of body water. In Table II, for example, are shown recent observations in men made by Keating and Albert at the Mayo Clinic (31). The values for the distribution-volume are quite anlogous to those obtained by other methods. Indeed they are sharp enough to discriminate between hypo- and hyper-thyroid patients as compared with normal men.

After an organic compound of iodine is administered, and as this material breaks down in the alimentary canal or within the blood stream or elsewhere, iodide is paid out progressively into the circulation and distributed through the body fluid. Therefore, whenever an iodine-containing drug is used, the fate of iodide itself immediately is involved in the total picture.

Once the iodide has entered the general systemic circulation, its subsequent history involves four major channels. From the circulation a goodly proportion of the iodine is taken up by the thyroid gland, which is a marvelous iodide trap. The activity of the thyroid in this respect can be measured by the use of tracer iodide, and Keating and Albert (31) have proposed the concept of "thyroid clearance" to indicate the volume of plasma that hypothetically could be freed completely of iodide per minute. Between the normal and the hypothyroid man there may be over a tenfold increase in this clearance rate. When amounts of iodide less than a hundred micrograms are administered to man, the proportion of the iodide which ends up in the thyroid may be over 70% in hyperthyroidism and frequently over 40% in normal man. As larger and larger doses of iodide are given, however, less and less is trapped by the thyroid gland, which soon becomes saturated.

**Renal Clearance.**—Competing with thyroid clearance is the "renal clearance" which accounts for the major portion of iodide excretion, as shown in Fig. 1. This iodide clearance is measured in precisely the same way as urea clearance has been measured for decades in accordance with the equation proposed by Van Slyke while at the Rockefeller Institute (32):

$$\text{Clearance} = UV/B$$

where $U$ is the concentration of iodide in the urine, $B$ the concentration of iodide in the blood, and $V$ the volume of urine produced per minute. Obviously the thyroid and the kidney compete with each other in the removal of iodide from the circulating plasma. Indeed, my former associate, Dr. Douglas Riggs, now at Harvard, has found that a normal man "clears" free of iodide about 40 ml. of plasma per minute (33). If the thyroid is hyper-active, as in exophthalmic goiter, it will predominate over renal excretion at least for a short time. Similarly

TABLE II.—APPROXIMATE VOLUME OF DISTRIBUTION OF INORGANIC IODIDE

[From Keating, A. R., and Albert, A. (31)]

| Group | Cases | Approximate Volume of Distribution: Method C,[a] Liters | Method D,[b] Liters | Mean of Individual Differences, Liters | Volume by Method D, Cc. per Kg. |
|---|---|---|---|---|---|
| Exophthalmic goiter | 16 | 32.0 ± 1.8[c] | 31.2 ± 2.2 | −0.7 ± 1.7 | 530 ± 43.8 |
| Euthyroid | 6 | 25.9 ± 2.9 | 26.0 ± 3.5 | +0.07 ± 0.8 | 350.2 ± 38.6 |
| Myxedema | 6 | 24.4 ± 2.7 | 23.9 ± 3.1 | −0.5 ± 1.6 | 352.8 ± 35.9 |
| Adenomatous goiter with hyperthyroidism | 3 | 25.3 ± 4.7 | 22.1 ± 6.4 | −3.2 ± 0.5 | 340.0 ± 39.3 |
| Adenomatous goiter without hyperthyroidism | 3 | 20.9 ± 1.9 | 20.9 ± 2.7 | −0.07 ± 1.0 | 316.0 ± 50.6 |

[a] Method C = Volume estimated by taking the value $\frac{1}{C_0}$, the reciprocal of concentration.

[b] Method D = Volume estimated by taking the value $\frac{\text{Clearance}}{Q_{wf} \times r} \times 60/1000 \times 100$. The mathematical symbols are explained by Fig. 1.

[c] The values given are the means and standard errors of the means.

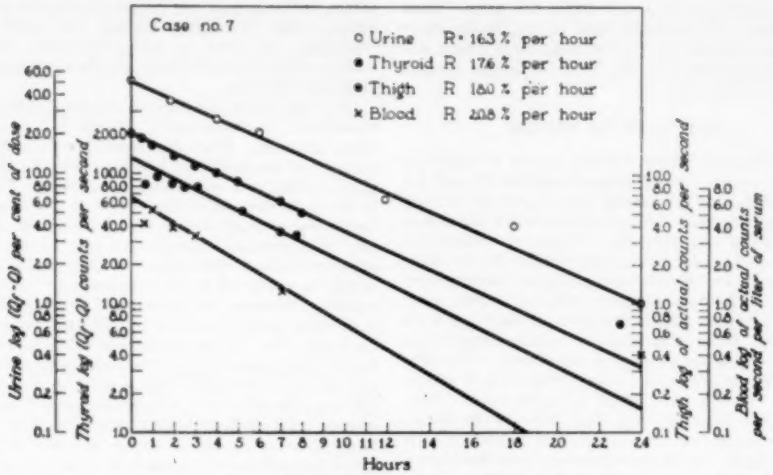

Case no. 7
○ Urine R = 16.3 % per hour
● Thyroid R 17.6 % per hour
● Thigh R 18.0 % per hour
× Blood R 20.8 % per hour
Urine by (Q-Q) per cent of dose
Thyroid by (Q-Q) counts per second
Thigh by of actual counts per second
Blood by of actual counts per second per liter of serum
Hours

Fig. 1.—Curves of urinary excretion, thyroidal accumulation, radioactivity in the blood, and radioactivity in the thigh plotted on a semilogarithmic scale. The significance of the interrelationship is shown here: it is seen that all four curves have approximately the same rate constant.
From Keating, A. R., and Albert, A. (31).

in Bright's disease, when the kidney is badly damaged, renal secretion may be relatively small. In myxedema, when the thyroid is largely scar tissue, the thyroid clearance will be insignificant. Ordinarily renal and thyroidal clearances together account for the major part of the fate of iodide.

**Body Fluids and Other Miscellaneous Tissues**—The remainder of the iodide is removed from the blood stream either in body fluids such as saliva and sweat, or by the miscellaneous tissues. For a few hours after the administration of a dose of iodide these miscellaneous functions account for anywhere between 10% and 30% of the administered drug. Ultimately, however, the degradation of metabolic processes turns back this iodide into the blood stream, and it must be lost either through the urine or in other excreta or secretions. A small amount is even lost in the expired air. Although in total amount this "pulmonary clearance" is relatively insignificant, after the administration of therapeutic doses of radio-iodide it amounts to an appreciable radiation. If one holds a Geiger counter under a patient's nose, with each expiration the milliammeter jumps and the monitor crackles. My associate, Dr. Gopal Karandikar, has evidence that this "pulmonary" clearance may be useful in the clinic in judging the concentration of radioactive isotope within the blood stream. For example, in a patient studied by Dr. Karandikar and me, 14 millicuries of radioactive iodine had been administered orally for the treatment of a thyroid cancer. Forty-eight hours after the ingestion of this medication, the total residual $I^{131}$ was estimated at slightly less than 700 microcuries. At this stage the patient exhaled radiation to the extent of almost 2 microcuries per breath while his blood serum ran parallel in specific activity. Like the dragons of old, which in mythical legends breathed forth fire, these modern patients all unwittingly exhale radiation!

## THE FATE OF ORGANIC COMPOUNDS CONTAINING IODINE

When one enters into as complex a topic as this, one realizes how much work remains to be done and how difficult it is to generalize concerning the behavior of the multitudinous and varied possible combinations of organic molecules containing iodine. In general, however, as a tentative working hypothesis, it may be possible to discern some properties which seem peculiar to organic compounds of iodine, whereas other properties are attributable chiefly to the particular organic complex involved. Of course some iodine compounds are highly insoluble and in grocery-store dosage would largely be excreted if given orally, or if injected intramuscularly would form solid masses acting locally as foreign bodies. Some of the old-fashioned surgical dusting powders such as thymol-iodide were of this type. It was expected that they would act either through a minimal solubility of a highly active substance or by local decomposition with the release of iodine in some form (such as hyperiodous acid) which might be effective in the immediate vicinity of its origin. Those compounds, like diiodotyrosine, which have a small but appreciable solubility, appear to be distributed fairly uniformly through body fluids with some adsorption on protein molecules. If enough of the material is assimilated, the organic compound ultimately may reach the urine and may even penetrate into serous fluids or into the cerebrospinal fluid. Because decomposition of such a compound inevitably occurs to some extent, however, the investigator must be wary of interpreting the finding of iodine in a certain body fluid or tissue as evidence that the original compound has remained intact. This distinction frequently calls for some rather ingenious microanalytical chemistry in order to distinguish between

the dissolved organic compound in low concentration and iodide itself.

With respect to the blood stream, the presence of these compounds is a constant source of difficulty to the thyroid specialist. This difficulty is of two types. First, the organic compound itself may be associated with the plasma protein and so give a spuriously elevated value for so-called "hormonal" iodine in the blood plasma. Secondly, even more subtle confusion may occur, as pointed out by Salter (34), and by Curtis (28). This is the tendency of iodide (in this case split off from the organic compound) to combine with the plasma protein in the course of time, thus yielding an elevated value for colloidally bound iodine. How to avoid the confusion thus created in clinical diagnosis is one of the important technical problems in practical endocrinology today. The effect is illustrated in Fig. 2, taken from some work

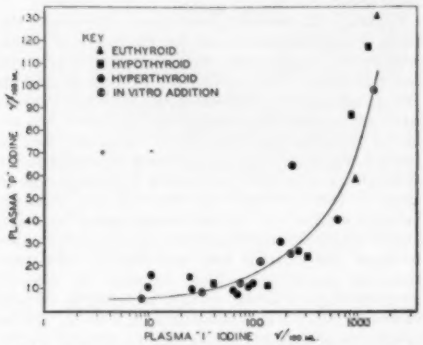



Fig. 2.—A spurious elevation of the protein-bound "P" iodine occurs when the inorganic "I" iodine is unusually high, as described in the text.

From Bassett, A. M., Coons, A. H., and Salter, W. T. (30).

performed in my laboratory nearly ten years ago (30). This false elevation of the protein-bound iodine is found in freshly shed blood. Curtis (28) has shown that a further increase may occur on incubation or standing of the sample in the laboratory. This last effect suggests the presence of an iodase enzyme system in blood, as hypothecated long ago by Blum (27).

One reason why it is important to know well the behavior of these iodine-containing drugs is that they may confuse the hospital chemist who is testing a given patient's blood for an excess of thyroid hormone. Figure 3 shows how well the protein-bound iodine in the blood plasma of man reflects the activity of the thyroid gland. In these 100 cases which I studied in Boston there was an excellent correlation between the analyses for iodine and the diagnosis. The erroneous report of a high organic iodine content might lead to a useless operation involving a border-line decision in diagnosis. Even iodized oil, injected into the spinal canal to delineate a possible tumor, may supply the blood with extra iodine for many weeks. A special chemical treatment is needed to avoid this confusion. Similarly, as shown in Figs. 4 and 5, Dr. Donald Munro and I found that "Skiodan" soon found its way from the spinal fluid into the blood plasma.

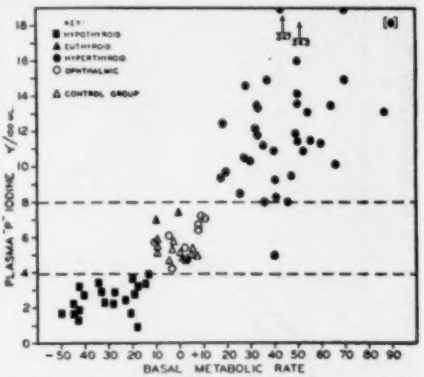



Fig. 3.—In two-thirds of the test cases studied, the clinical diagnosis and the basal metabolic rate were compatible, as shown in the figure. Plasma protein-bound iodine values are given for these cases and for 10 euthyroid controls.

From Salter, W. T., Bassett, A. M., and Sappington, T. S. (34).

An important method of studying such mixtures of natural iodine and pharmaceutical iodine is the use of radioactive iodine. To this end my associate, Dr. Paul Block, Jr., has introduced radio-iodine into certain chemical compounds. For example, radioactive iodide has been introduced into diiodotyrosine and other related phenolic substances by two methods. First by exchange, wherein the phenol-containing compound is allowed to remain in solution with radioactive iodide ions under conditions of temperature and $p$H laid down by Miller, Anderson, Madison, and Salley (36), and by Salter (35). Under these conditions a high proportion of the radioactive iodide enters into the molecule by exchanging with stable iodine already present. Direct iodination has also been employed. In this case the radio-iodide was converted to radio-iodine either by exchange or by oxidation with iodate, and the resulting iodine introduced into the uniodinated molecule by usual synthetic procedures.

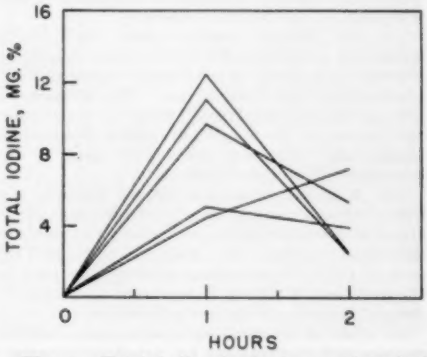



Fig. 4.—Total iodine in human cerebrospinal fluid after intrathecal instillation of sodium salt of mono-iodo-methane sulfonic acid.

From Salter, W. T. (34).

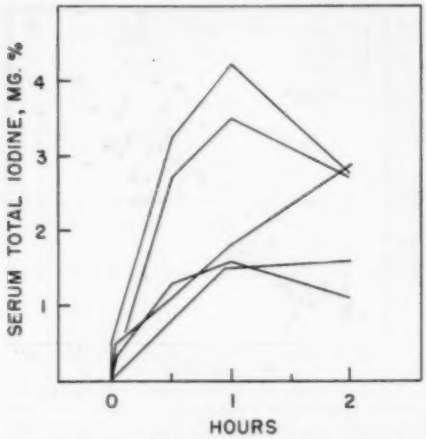



Fig. 5.—Total iodine in human blood serum after intrathecal instillation of sodium salt of monoiodomethane sulfonic acid. Excerpt from data obtained in collaboration with Dr. Donald Munro. From Salter, W. T. (34).

Radioactive thyroxine has been prepared by direct iodination (37) and by using the exchange method by Frieden, Lipsett, and Winzler (38). Since it would appear that both of these methods would favor the entrance of radioactivity in the phenolic ring of thyroxine rather than in the inner ring, these workers also prepared a sample of thyroxine in which the radioactivity would be expected equally in both rings. They resorted to the expedient of producing radioactive casein, allowing it to undergo the now familiar oxidative process, and hydrolyzing the resultant thyroxine-containing protein.

**The Thyroid and Organic Iodine.**—At the present time there is *no* evidence that the thyroid can utilize organically bound compounds of iodine. Even in the case of diiodotyrosine, current work indicates that this must first be split into iodide before the thyroid can take it up. Within the gland itself there occurs a complicated sequence of enzymic reactions which can be summarized as follows:

(*a*) An iodinase enzyme system traps iodide within the gland at a differential concentration of several hundredfold, or even several thousandfold, above that of the blood stream. This initial complex can be dissociated readily either by coagulating the protein or by use of an enzymic poison like thiocyanate. Figure 6, taken from work in my laboratory, illustrates this effect.

(*b*) A periodase enzyme system elevates the iodide so trapped to an energy level equivalent to the status of elementary iodine and allows it to combine with diiodotyrosine. This stage can be blocked by some of the common goitrogenic drugs now used in the treatment of thyroid disease, such as thiouracil, propylthiouracil, and certain imidazolines.

(*c*) Two of the resulting diiodotyrosine radicals combine to form thyroxine, i.e., tetraiodothyronine. Whether an organic compound will ever be found which can penetrate the thyroid cells directly and serve as an intermediate in this sequence remains to

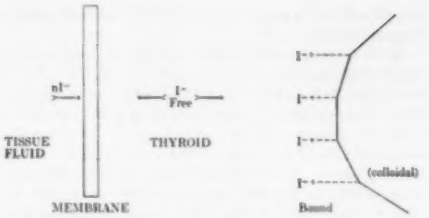



Fig. 6.—From Salter, W. T., Cortell, R. E., and McKay, E. A. (44).

be learned. It would be interesting in the study of thyroid disease if one could short-circuit the sequence by anticipating one of the synthetic steps in the thyroid's internal economy, but this has not yet been done.

In brief, the thyroid gland seems to depend entirely upon inorganic iodide for its source of iodine wherewith to make thyroxine. The gland is a rugged individualist and prefers to start from the ground up and do all its own synthetic work! In these modern days the availability of radioactive iodide has allowed physicians to take advantage of this fact in two general ways. In the first place, through the use of small test or tracer dosage they have been able to listen to the activity of the thyroid as it picks up iodide, (see Fig. 7). In the second place, by using highly active therapeutic doses, they have been able to trick the thyroid into assimilating miniature beta-ray generators which destroy the gland's parenchyma. The use of this material in certain thyroid cancers is illustrated in Figs. 8 to 12. These specimens of thyroid cancers were removed from the tumors of patients encountered in Connecticut.

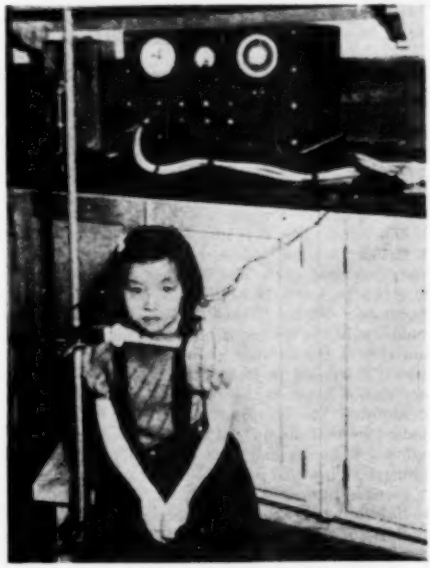


Fig. 7.—From Hamilton, J. G. (42).

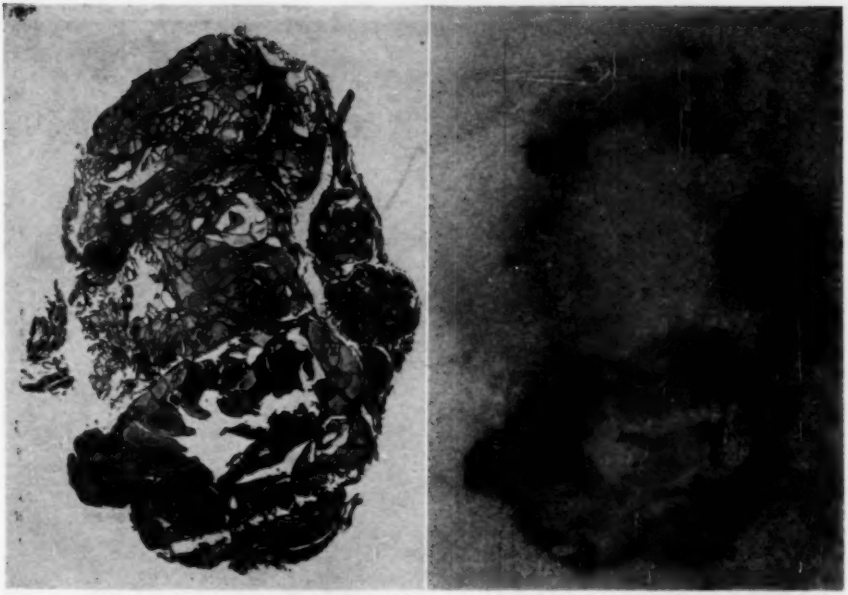


Fig. 8.—Homologous sections of tissue from patient E. S. showing (left) the ordinary histological section stained with hematoxyline-eosin and (right) radio-autograph from the same section.
From Salter, W. T., and Johnston, Mac A. (43).

These figures show how heterogeneous thyroid cancers are, not only among a group of these, but also within a given "lump." These pictures, it will be noticed, are in duplicate. The left-hand version shows the usual stained microscopic section as photographed in daylight. The right-hand version is a "self-portrait" made by each section as it lay on a photographic film in the dark. Because of the radiant energy extruded from these "tagged" specimens, they form a radio-autograph, so-called.

**The Liver.**—One of the most important features of many compounds of iodine is the role which the liver plays in their metabolism. Whether administered intravenously or absorbed from the intestine by way of the portal circulation, these compounds tend to be trapped in the liver substance. Figures 13

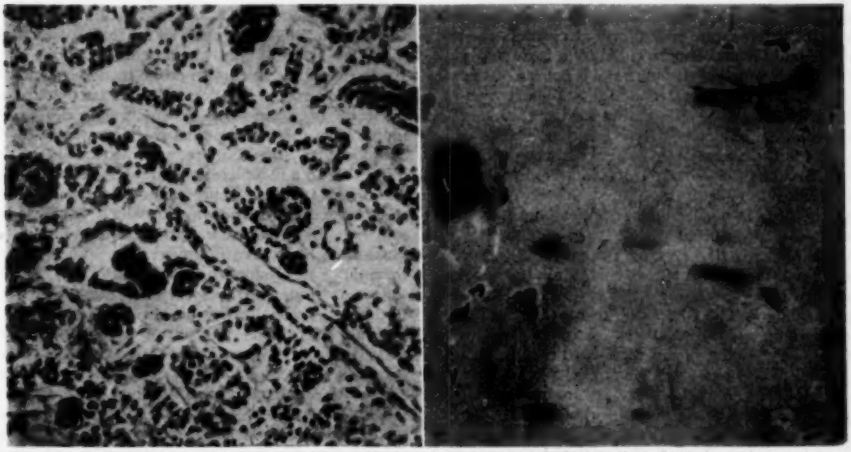


Fig. 9.—Homologous sections from patient N, showing poor fixation of radio-iodide, by a fetal adenoma of the thyroid. On the left is the ordinary histological section stained with hematoxyline-eosin; on the right is the radio-autograph of the same section.
From Salter, W. T., and Johnston, Mac A. (43).

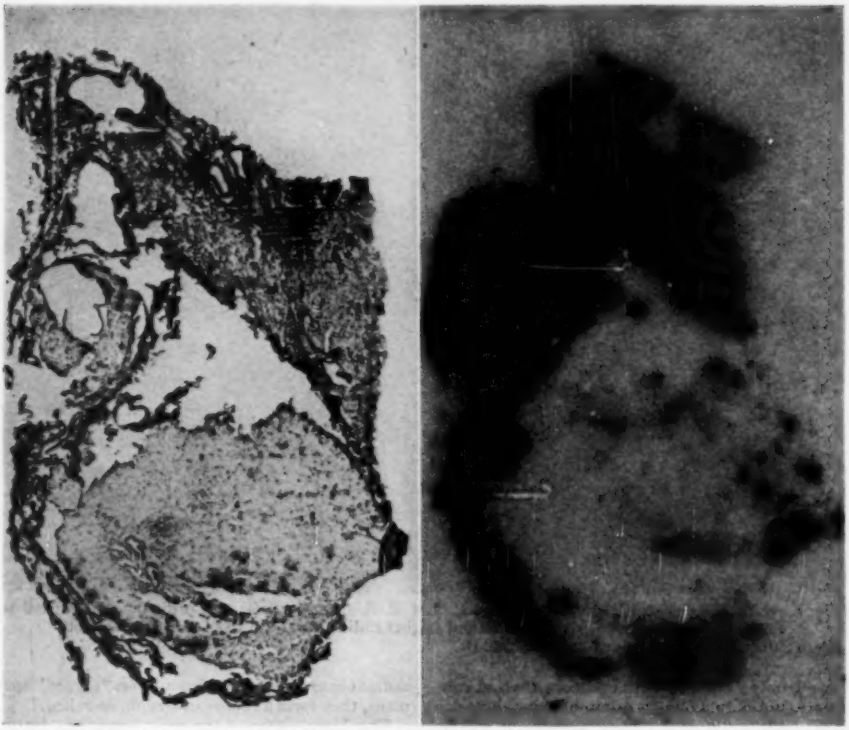


Fig. 10.—Homologous sections of tissue from patient N, showing varying fixation of radio-iodine in different types of tissue, carcinomatous and necrotic.
From Salter, W. T., and Johnston, Mac A. (43).

and 14 illustrate this phenomenon for diiodotyrosine and for "Priodax," respectively. The phenomenon is as if the liver were endeavoring to protect the rest of the body from being invaded by a toxic material. Forthwith, much of this material is poured out in the bile, back into the intestine. Consequently much of the original iodine is eliminated with the feces. To a considerable extent the liver decomposes the compound in the course of its excretion through the bile. In the case of thyroxine, for example, even rather high doses appear in the bile, completely destroyed. As the dose is pushed higher and higher, however, more and more of the original iodine complex appears unchanged. Evarts Graham (23) and his colleagues took advantage of this fact in the development of their "Graham test" for visualization of the gall bladder. The compound commonly used (e.g., tetraiodophenolphthalein) is relatively opaque to X-rays by virtue of its high iodine content, and thus it enables the roentgenologist to visualize the gall bladder. As this material is reexcreted in the bile, of course some of it is absorbed again. Thus a sort of continuous cycle occurs. In the meantime there is constant loss of the material through the intestine and through the kidney. At the same time the drug is undergoing decomposition to a certain extent and iodide is being released.

With all this complex chemical maneuvering going on simultaneously, it is rather difficult to interpret the meaning of a single analysis for total iodine in the blood or urine at any given moment. One must study the whole picture in order to understand the metabolic processes concerned. In particular, one must be prepared to separate organically bound iodine from inorganic iodide which may arise by decomposition. Furthermore, one must be able, if one wishes to do a complete job, to distinguish between the original organic compound and the partial degradation products thereof, in which some iodine still remains attached to carbon, either in the original molecule or in a fragment of it. The chemical formula (V) of Iodophthalein Sodium, U. S. P., also known as "Iodeikon," was formerly used extensively in the X-ray visualization of the gall bladder.

**Renal Excretion.**—In addition to iodide which results from decomposition, in the case of certain compounds there is often a considerable renal excretion of organically bound iodine. The extent to which this occurs is partly dependent upon the ease of decomposition of the organic molecule. A considerable number of organic molecules are known which are excreted in large measure by the kidney. Some of these, as originally described by Mosenthal (39), may be used simultaneously as a test of liver

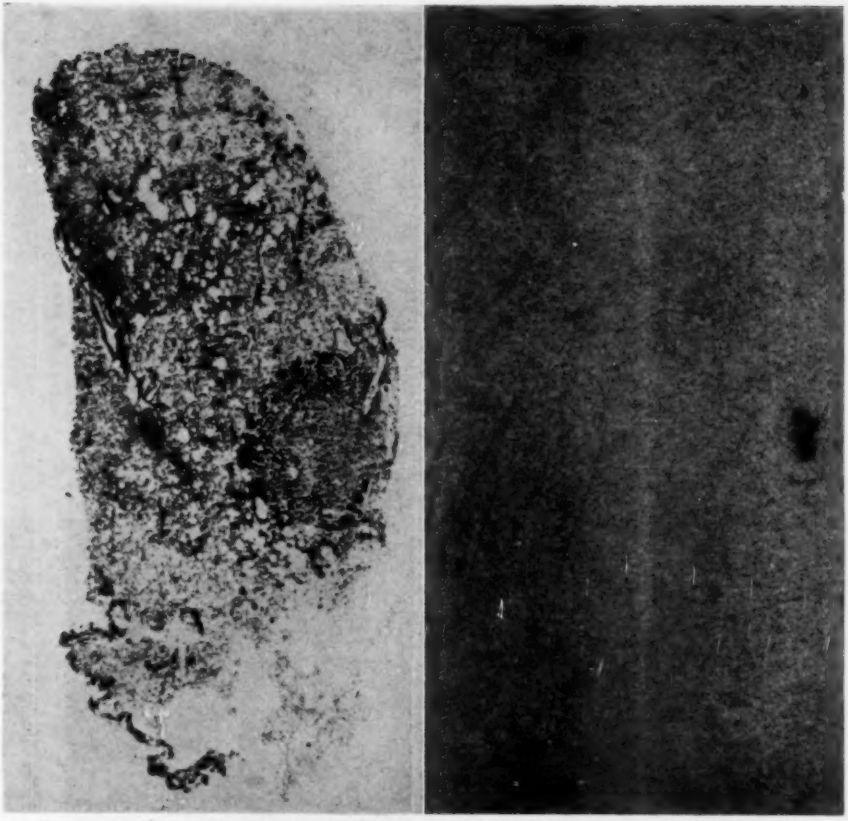
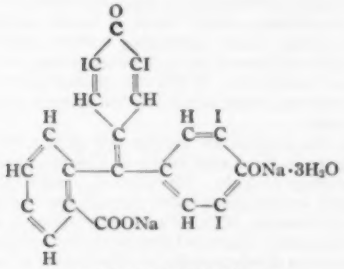


Fig. 11.—Homologous sections of tissue from patient V showing (left) lung metastasis, (right) radio-autograph of the same. Note that several months earlier this metastasis failed to fix radio-iodide and that later the fixation (although poor) became definite.
From Salter, W. T., and Johnston, Mac A. (43).



Iodophthalein Sodium
(V)

and of renal function. The more modern compounds, however, have been developed primarily for use in the urinary tract. Not only are they used in the clinic to visualize the urinary passages, but they are used by physiologists to test kidney function. As described by Homer Smith (25) and others, they constitute a convenient means of studying the activity and the mass of tubular tissue because they are excreted in large measure by tubular secretion. Table I, taken from Smith and Ranges (25), describes the properties of five such compounds. These are "Diodrast," "Hippuran," "Iopax," "Neoiopax," "Skiodan." As will be described presently, another compound known as "Priodax" has similar properties.

## RELATION OF CHEMICAL STRUCTURE TO METABOLIC FATE

In the present state of our knowledge it is very difficult to compare various iodine compounds with respect to their stability in the organism. Compounds as widely differing as ethyl iodide, thyroxine, and tetraiodophenolphthalein are used in medicine regularly. They all yield a certain amount of inorganic iodide in the animal organism. In the case of thyroxine, to my knowledge, no one has ever isolated intact thyroxine from the urine, but the

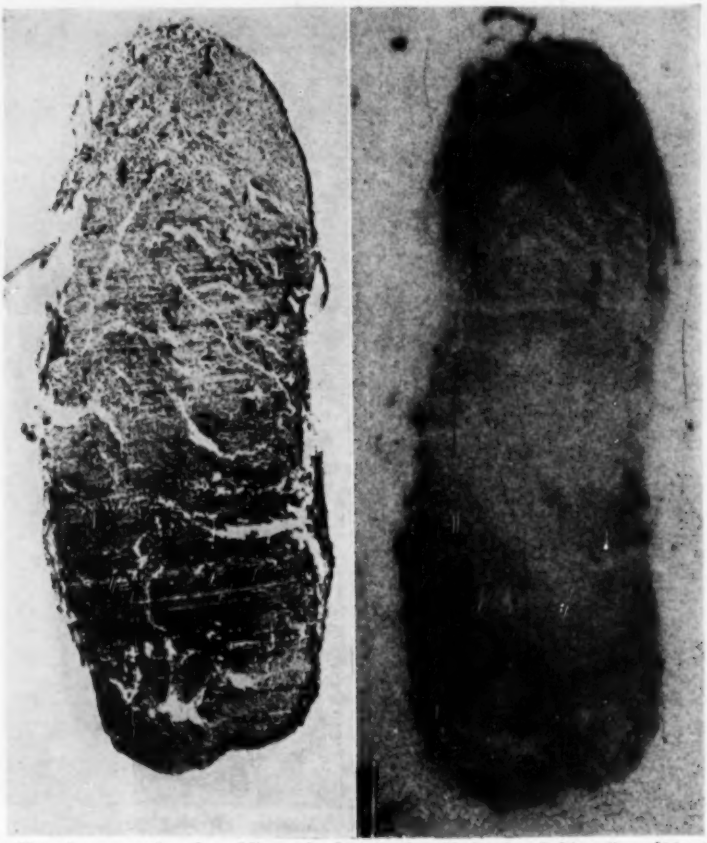


Fig. 12.—Homologous sections from hilar nodes from patient V showing (left) ordinary histological section and (right) radio-autograph of the same.
From Salter, W. T., and Johnston, Mac A. (43).

drug is so powerful that even stout men can endure only a relatively few milligrams at a time. Its decomposition product or precursor, diiodotyrosine, likewise is readily decomposed. Because it is less active pharmacologically, larger doses may be given up to the point that the unaltered organic substance can be found in the urine as well as in the blood stream. Even so, a considerable portion of it is split into inorganic iodide.

The amounts of Iopax, i.e., "uroselectan," and of tetraiodophenolphthalein which are given for X-ray visualization are very large in comparison with the ordinary metabolic consumption of thyroxine or diiodotyrosine. Consequently, it is not surprising that a considerable proportion of these materials is excreted unchanged. This finding does not necessarily mean, however, that these materials are less susceptible to decomposition in the body. It means simply that bodily mechanisms which ordinarily would decompose these compounds have been overwhelmed temporarily. It will be desirable to make a careful study of the fate of widely differing types of organic chemical compound at the same level of molecular concentration in body fluids and in molecular-equivalent doses. Such a study ultimately will disclose many interesting features about the stability of different types of iodine linkage in varied organic structures. It will also disclose preferential excretion or concentration in the several organs of the body.

At the moment an investigation of this sort is in progress in the Laboratories of Pharmacology and Toxicology at Yale. For instance, a series of compounds, largely contributed through the courtesy of Dr. Henderson of Schering Corporation, is under investigation. These substances are derived theoretically from diiodotyrosine by substitution of various inherent constituent groups. Into these molecules not only stable but radio-iodine has been incorporated so that the tracer technique can be used as well as routine analytical methods. Among these compounds are included the following: Cyclohexyl diiodohydroxyphenyl propionic acid (VI); Phenyl diiodohydroxy cinnamic acid (VII); and the ethyl ester of phenyl diiodohydroxyphenyl propionic acid (VIII).

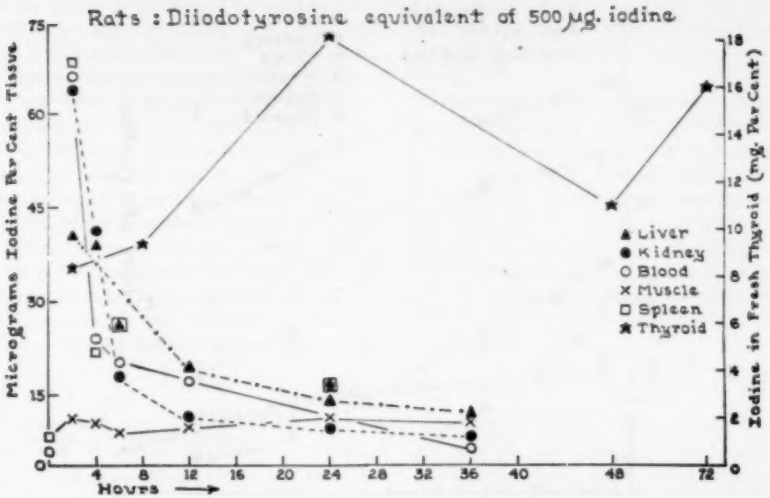
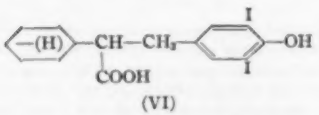



Fig. 13.—The iodine distribution in various rat tissues is shown after the intraperitoneal injection of "500 micrograms iodine as diiodotyrosine" at various intervals of time. The thyroid value is charted in milligrams per cent on the right ordinate; values for the rest of the tissues in micrograms per cent on the left ordinate. The kidney and blood serum show higher initial contents than does the liver. After such high doses the protein-bound iodine rises more than does the iodide fraction. With smaller doses the reverse is true.



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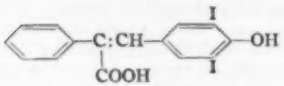
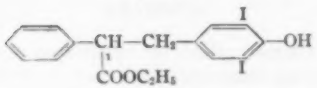


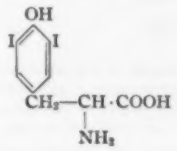
(VII)



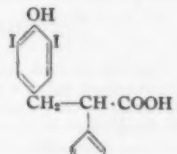
(VIII)

Their metabolic fate is being contrasted with that of the mother or prototype substance, diiodotyrosine. Figures 13 and 14 illustrate the behavior of "Priodax" [β-(4-hydroxy-3,5-diiodophenyl)-α-phenyl propionic acid] as compared with diiodotyrosine when both are injected into litter-mate rats intraperitoneally at the same molecular dosage (40). The concentration of the "Priodax" in the liver at the end of three hours is of special significance. The fact, however, that some concentration also occurs in the kidney tissue indicates that this substance, like the "uroselectan" ("Iopax") or "skiodan" group of materials, may also be used to study renal function (41).

It will be observed below that this "Priodax" (IX) is a drug made (on paper, at least) from the natural metabolite *diiodotyrosine* (X) by substituting a phenyl group for an amino group.



Diiodotyrosine
(X)



"Priodax"
(IX)

A chief result of this substitution is a predilection for the biliary route of excretion, whether the material be administered orally or by intravenous injection. Like its natural relative diiodotyrosine, however, it still preserves a trend toward renal excretion as well. This is shown by the experimental results already given in Figs. 13 and 14.

Some of these derivatives of diiodotyrosine also share the properties of other organic iodine compounds previously mentioned. For instance, phenyl diiodohydroxy cinnamic acid has interesting properties as a remedy against the organism which causes amebic dysentery. In this respect it recalls the effect of "Chiniofon," which has already been discussed. Likewise, cyclohexyl diiodohydroxyphenyl propionic acid shows bactericidal action against Shigella dysentery organisms in cultures, at least. In general, therefore, this group of chemical congeners illustrates how drugs of different actions may be formed by altering the chemical constitution of a single parent molecule. Obviously such derivatives will retain many of the metabolic peculiarities of the parent substance.

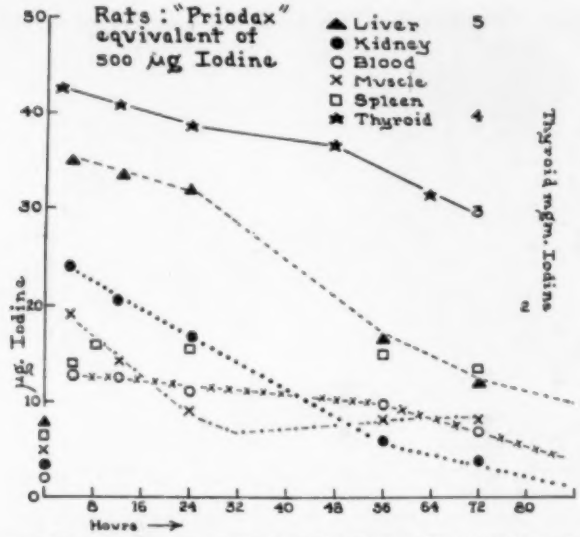



Fig. 14.—For comparison with the data on diiodotyrosine given in Fig. 13, this graph shows the relative distribution of iodine in micrograms iodine as "Priodax," administered I.P. The tissue concentrations are given on the left ordinate; those for the thyroid on the right ordinate. On such high doses the compound raises the "protein-bound" fraction of iodine more than the "iodide" fraction in tissues. In smaller doses it is the iodide fraction which rises higher. Note that in Fig. 13, the thyroidal iodine concentration is adjusted for a hypothetical 100 Gm. of rat. In Fig. 14, the iodine is that per 10 Gm. of wet thyroid, as found in the 300-Gm. rats studied.

## DISCUSSION

Thus far we have spoken largely of the empirical fate of certain iodine-containing complexes and their particular predilection for certain organs or parasites. We have also mentioned the possibility that some are more susceptible to destruction by protoplasmic enzyme systems than are others, and that this fact may be used either negatively or positively for therapeutic purposes. There is one further aspect of the incorporation of iodine into organic compounds which has been very little explored as yet. This is the development of molecular competitors which may serve as blocking agents in normal metabolic processes. This underhanded trick also may be played against the bacterial or plasmodial cell. Indeed it has long been a puzzle why some of our best antimalarial drugs contain halogen, i.e., chlorine, in the molecule. Doubtless there will be found other parasiticides and perhaps antibacterial agents in which an iodinated molecule is highly effective. Already iodine has appeared in such compounds as "Vioform," so effective against pseudomonas or lamblia-like organisms.

We noted at the start that the most important iodine-containing drugs *used for internal action* could be classified arbitrarily as (*a*) thyroid drugs and (*b*) nonthyroidal. We must now add the reservation that some drugs appear to straddle this distinction. Diiodotyrosine plays an important role in the internal economy of the thyroid gland and in the chemist's synthesis of thyroxine. When simple substitutions are made in its constituent chemical radicals, however, it becomes a diagnostic aid in liver problems or even a remedy for amebiasis.

Moreover, the parent molecule diiodotyrosine is formed whenever tincture of iodine meets blood or flesh or bacterial protoplasm. Thus step by step, the pharmaceutical chemist and the pharmacologist watch the gradual evolution of new drugs by simple but progressive changes in well-known molecules. As in the parlor game, played by young ladies at house parties with folded paper, they are often astonished at the final result produced by random additions to the original picture!

## SUMMARY

In summary, then, the metabolism of iodine-containing drugs within the body resolves itself first of all into the history of inorganic iodine and of organic iodine. Whenever an organic compound is administered to a mammal, varying amounts of iodide are liberated by decomposition, so that one is never rid of the question of *inorganic* metabolism. Our most potent drugs, e.g., thyroxine, are so completely decomposed that their final degradation products as thus far detected have consisted entirely of the iodide ion alone.

With regard to the fate of organic iodine compounds, at the moment they can be divided into two great classes, i.e., first, those connected with the internal economy of the thyroid; and secondly, those which are more strictly pharmaceutical in nature. In the first group, in addition to

iodide, the chief compounds to be considered are diiodotyrosine and thyroxine, together with some of their simpler derivatives. In the latter group a great variety of compounds is possible. Apart from local or parasiticidal action, however, thus far most of them are distinguished by their concentration in the liver and in the kidney. In connection with their hepatic concentration they serve a useful purpose in visualizing the gall bladder and biliary passages by virtue of the high radio-opacity of the constituent iodine atoms. The same radio-opaque effect is also applicable to the urinary passages, but in addition such iodine-containing materials may be used to measure tubular function or tubular mass. This same radio-opaque effect has also been used in other situations, notably in the spinal canal where the detection of tumor masses or of blockage is important.

Because the persistence of these molecules in intact form is a matter of considerable importance if their pharmaceutical action is to be preserved, careful studies of the types of compound which are least liable to immediate disintegration within the organism are indicated. Similarly more careful and extended studies are needed of the effect of introducing iodine into some of the better known drugs, in order to ascertain whether their potency or their specificity can thereby be enhanced.

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## WHO MAKES IT?

The National Registry of Rare Chemicals, Armour Research Foundation, 33rd, Federal and Dearborn Streets, Chicago, Ill., seeks information on sources of supply for the following chemicals:

Sphaerophorin
Atraric acid
Divarin
Pulvinic acid and methyl ester
L-α-Glycerylphosphorylcholine
*d*-Laudanosine
Canadine
Barbatinic acid
4-Amino-8-nitroquinoline
Obtusatic acid
Divaricatic acid
Atranorin
Shikimic acid
2,3-Dimercaptopropyl ethyl ether
2-Methyl-8-hydroxyquinoline
Muscarine
Bulbocapnine
Adenine thiomethyl pentoside
Phosphorylthiocholine
L-Mannose

# Cooperative Development of Scientific Standards*

By GEORGE D. BEAL†

DURING the Buffalo meeting of the AMERICAN PHARMACEUTICAL ASSOCIATION in August 1924, Frank Taylor and Paul Snyder invited me to tell a group of control chemists about some research that I had under way at the University of Illinois on a quantitative alkaloidal reagent. Although the reagent still shows some promise, it rather resembles an unsecured promissory note. The group to whom I was speaking, however, and its planned purpose, have shown the security of a first mortgage. When one subtracts 24 from 49 the remainder is 25. This, in years, is a quarter-century. Twenty-five years is not a long period of time, but there is something awe-inspiring about a century, sometimes savoring of history, so that a fraction as substantal as a quarter has dignity about it.

Although you have an informal membership roll and operate with nothing resembling a constitution or a bylaw, you have followed a steady course of action, have grown in numbers, and have created a boundless respect for yourselves. Yours is, to my mind, the ideal scientific organization. You know why you come and you keep on coming until you finish your job.

We have other seriously minded scientific organizations in this country, scholarly, as you are, some quite practical, others rather academic. You have a very close community of interest, and I think you excel nearly all other analytically minded groups in the extent to which you speak with a common tongue, and the extent of your friendliness one with another. It is likely that the few of you who organized this group back in 1924 had some misgivings about the outcome, and hoped that you were engaging in more than wishful thinking. You have, on the contrary, demonstrated that it is profitable for people having common interests, even though competitive, to get together for a discussion of common problems, to lay a few cards on the table, and sometimes to borrow an older shoulder for a bit of weeping.

It is difficult to say that pharmaceutical industry was the first to make any use whatever of the laboratory in manufacturing control, but we are certain that this was the first industry to introduce systematic methods of laboratory control, although some of its members have but recently joined the procession. In some of the pharmaceutical houses, and in some of the colleges of pharmacy, very real scholars were developed at an early date. I had the curiosity to inquire as to when the AMERICAN PHARMACEUTICAL ASSOCIATION began to receive scientific papers on its programs, rather than those that usually come at the beginning of such an organization when most speakers tend to view with alarm or point with pride. The ASSOCIATION took form from a conference of druggists held in New York in 1851 and the first stated session occurred in 1852 in Philadelphia, the proceedings forming but a skimpy pamphlet. But the proceedings of 1858 make a substantial volume, and in addition to a number of papers on professional problems and the relation between pharmacists and physicians, that would have been equally pertinent if read at the Jacksonville meeting last April, there were excellent and technical papers by Dr. Edward R. Squibb and Dr. Frederick Stearns. As these gentlemen then were not beardless boys, we say with assurance that we have had over a century of scientific pharmacy in the United States, enough to give courage to other industries that have questioned the wisdom of expenditures for research and control.

The history of the United States Pharmacopœia has been related many times, and before the 14th decennial convention adjourns next May we will be more fully bored thereby. From U. S. P. VI, in 1883, we have had a pharmacopœia that in style suggests that currently official. Its immediate predecessor, U. S. P. V, included some critical data and tests. The first National Formulary, begun in 1888, proposed to carry the plan of standardization further into medicinal formulas. In those days the members of college faculties took perhaps a more prominent part in state association work than now, so that some of the state laws relating to the practice of pharmacy used the criteria set forth in the Pharmacopœia and Formulary official at the time of investigation as quality standards for drugs being sold. The successful use of these volumes as state standards rendered much easier their adoption as Federal standards in the law of 1906.

The PROCEEDINGS of the AMERICAN PHARMACEUTICAL ASSOCIATION show that during the scientific era of American pharmacy reports on re-

* An address delivered at the 25th Anniversay Meeting of the Combined Pharmaceutical Contact Committee, Washington, D. C., October 7, 1949.

† Assistant Director, Mellon Institute of Industrial Research, Pittsburgh, Pa.

search progress have been quite proportionately distributed between educational and industrial sources. Somewhat the same proportionate distribution appears as we look over the names of those active in pharmacopœial and formulary revision, whether as active members of committees or as collaborators. The cooperative measures that have resulted in the production of our official standards for medicinal agents are, I believe, unique in their democracy, and their acceptance as state and Federal standards is a tribute to the scholarship and integrity of their makers that is paid by no other government.

It would be difficult, and it is not pertinent, to attempt to list here all of the collections of scientific and technical standards that are produced in this country by cooperative groups. Two of unusual prominence and utility that must not be overlooked, however, are those of the Association of Official Agricultural Chemists and the American Society for Testing Materials. We have become very much standards-conscious in the United States, as evidenced by the numbers of commodity standards and accreditation standards extending from the acceptance standards of the Council on Pharmacy and Chemistry of the American Medical Association to the standards for accreditation of colleges of pharmacy set forth by the American Council on Pharmaceutical Education. They include informative standards, such as those calling for informative consumer labeling of retail commodities and standards mutually agreed upon for membership in scientific and professional societies and academies; industrial standards, such as those agreed upon between buyer and seller; and regulatory standards, or those which determine the right of an article to enter into a particular field of commerce or grant to a person the right to engage in practice of a profession. The validity of any standard or group of standards can properly be determined by the extent to which it satisfies some factor of welfare, using "welfare" strictly in its nonpolitical sense.

Standards that are conditioned upon welfare include those that secure safety, efficacy, and proper return for one's money. Therefore, such standards are concerned with the purpose of the product, process, or occupation and are "end-use" standards. In fact, it is difficult to conceive of a meaning of the term "standard" that does not involve some question of usage. I should say that substantially the same principles apply to standards for commodities regardless of the end-use of the substance. The terms of the standard, however, will depend upon the critical character of the end use.

An important problem in the development of any standard is to determine just how critical that standard shall be. In theory, the user should be the best judge of what is required. By this I mean the actual user; not the self-appointed representative, the professional "consumer," strong in the heart, with good intentions and weak in technical knowledge, who is ever ready to appear before legislative committees or women's clubs or to sound off in the press. The reasons that determine the need for any proposed system of standards are very much like the screening test that serves while outlining an industrial research project. Industry, in its search for knowledge, should try to determine: (*a*) whether the proposed search is for something essential to its well-being; (*b*) something that it ought to know; or (*c*) merely for interesting information, i.e., of academic interest. And it should budget its research expenditures in precisely that order. But while caring for its special needs, industry owes something to the science and technology that has made its growth possible. Hence, if its resources permit, it is the responsibility of industry to make some contribution to the reservoir of general technical knowledge. In like manner, it is a responsibility, really a privilege, of industry to participate in making standards for that industry.

In the last analysis, the producer who applies the best in technical skill and knowledge to the development and manufacture of his product is the one able to make the soundest recommendations as to what the standards for that product should be. The producer, on the other hand, is not as a rule in the best position to observe everything that occurs during end use of his product by the consumer. Furthermore, the consumer is not always technically able to detect degrees of unsatisfactory performance by the commodity. It, therefore, becomes the function of government, in theory composed of producer and consumer, to arbitrate. This arbitration is called regulation, but ideally is approached from the point of equity, not compulsion.

While participating in the cooperative development of drug standards, there has been for me a certain advantage in being on the outside, with no axe to grind. Thus it has been possible to look in, around, or at any problem, and, viewing it somewhat disinterestedly to get a better idea of its relation to the industry. It has also been easier to keep in mind the fact that all of those on both sides of the fence are still human beings, with the customary frailties. One sees that employment in a government laboratory does not confer infallibility, and that manufacturers do not always think in selfish terms.

One can also observe that profit is more likely to accrue from what one does for himself than what is secured for him by legislation. There is no denying that survivorship in industry is through a battle of wits, but those most likely to survive in this battle are the ones who have as one of their leaders old General Honesty.

I have been trying here to get to the point that the development of standards for commodities ought not to be approached as a competition, because I often encounter the view, which I think is entirely wrong, that standards should be kept at a level where the producer can barely comply with them, the champion of the standards apparently believing that he is insuring industrial progress thereby. This might be justifiable when the standards of an industry are low, but when, as in most industries, those standards speedily balance consumer needs they should be stabilized, at least until there is some economic evidence of the need for re-evaluation of a standard. Competition in standard making between producer and consumer sometimes leads to insistence upon a standard that can serve no useful purpose with reference to either durability or safety.

The principles to be observed in the establishment of a standard are much the same whether they relate to fixing the numerical value of the standard or agreeing upon the method by which compliance is determined. Perhaps the thing that has astounded me most is the lack of appreciation that some otherwise intelligent people have for a standard method of testing. I had a very brilliant man, not a pharmaceutical chemist, working with me, who was in constant difficulty with our client because the two could never agree upon the characteristics of the product with which he was working. He was much distressed, but when questioned about the certainty that he had observed all of the details of the standard method, which we knew the client was using, said that he thought it a reflection upon the ability of a scientist to require him to adhere to a standard method. Most of you will appreciate the extent of the difficulty he was meeting when you recall how two or more people using a supposedly standardized procedure on aliquots of a referee preparation have failed widely to agree. Probably Frank Taylor's digitalis tincture of around fourteen years ago is one of the classic examples. Even the most highly trained specialists in an analytical method may vary among themselves in their performance of minor manipulations, that are supposedly uniform with all of those "skilled in the art," unless they have actually worked side by side as members of an athletic team would play.

Standards should fit the need that the commodity is expected to satisfy. If the commodity has a variety of uses, and but one set of standards is to be drafted, those standards may be more critical than where only one specific use is indicated. Probably the most critical standards in the commodity field are those for all-purpose reagents. On the other hand, a reagent for one particular use may be very lenient except with respect to the determination in question.

The General Notices of the Pharmacopœia speak thus of the standards therein: "The standards prescribed in this Pharmacopœia apply to the substances, and to the preparations and their ingredients therein named when intended for medicinal use, and when bought, sold, or dispensed for this purpose or when used in the tests and assays herein provided." The corresponding statement in the British Pharmacopœia is "The standards of purity and strength of the Pharmacopœia apply to articles which are intended for medicinal use but not necessarily to articles which may be sold under the same name for other purposes." While this perhaps does not cover scope like an umbrella, as does the U. S. P. phraseology, it is to be admired for the clarity and conciseness of its disclaimer of anything beyond drug use.

It is often difficult with the layman, and next to impossible with the professional consumer, to explain why medicinal standards are not of necessity the highest standards of purity. The purity of most medicinal agents compares favorably with the soap that is $99^{44}/_{100}$ per cent pure. Usually that is not a difficult condition to meet commercially. But we are greatly concerned about the remaining $^{56}/_{100}$. This is a far closer tolerance than could be established by a biological assay, which is the only analytical procedure that may bear a relationship to therapeutic value. But in this fraction of a per cent may be found all of the traces of other compounds that cause inelegance, deterioration, or, in some instances, have an adverse effect upon the health of the patient. There may also be some element or radical present in that small percentage, itself harmless but occurring as a by-product of the manufacturing operations, that serves as an index of the care in manufacturing or the degree of purification.

Professional opinions differ widely as to permissible amounts of various impurities. The burnt child dreads the fire. Britain, having at one time suffered from a mass arsenic poisoning that came from an adulterated food, beer, to be exact, is far stricter than we in the matter of arsenic tolerance in medicinals, despite the fact that no one person consumes a drug to the extent that a food is taken. We must, of course, not speak in too great generalities, since drugs like sodium chloride

and dextrose are transfused in quantities comparable to food, and hence must be held to very strict standards.

Arguments over allowable limits of trace impurities may descend to mere quibbling. One manufacturer by some trick of process or raw material may keep the limit lower than another. If the products of the two manufacturers are equally efficient otherwise, equally safe and equally stable, economy to the buying public may be served by a generous decision in establishing a tolerance. After all, standards in general are to promote efficacy, not monopoly.

It is in assay methods that the spirit of competition runs riot. One's confident ability to devise the best assay is as sacred as his claim to the supreme qualities of the steak he broils on his garden grill. Probably we have few, if any, perfect assays, but in many instances there are two or more of which one could be drawn from a hat without impeaching the integrity of the product or the standard compendium. There are a few criteria that may be set down here, referring of course to assays for pharmaceutical purposes.

1. The assay should be as nearly as possible representative of supposed therapeutic value. This may be secured by: (*a*) a procedure that isolates or identifies the known active principle by an entirely characteristic reaction or (*b*) by measuring the characteristic physiological effect. The lack of an entirely characteristic reaction may be countered by negative tests for substances simulating the chemical effect. The U. S. P. Thyroid assay is not definitive, but a histological description of dry thyroid tissue and a qualitative test for soluble iodides make it more difficult to offer a factitious product.

2. Of two methods having approximately equivalent end points, or accuracy, the decision should be in favor of simplicity.

3. Choice of modifications where judgment may be based upon the degree of precision obtained should always be kept within practical bounds.

Scientific standards almost without exception are for the use of many people, and there are as many possibilities of misconception as there are users of a standard. Therefore standards must be developed out of experience. We as experimental scientists, if analysts may be so dignified by such a term, know how fallible one person may be. My experience alone may be but a series of incidents or coincidences. When I first make a motion I take the first step in developing a habit. If, ignorantly, I make a wrong motion and am not corrected, I begin to develop a bad habit. If I take two samples of an unknown of approximately the same weight, and treat them alike, even though there is an error in my treatment my results should agree closely but will be in error. If I use substantially different sample weights but perform all other operations similarly, my data, by lack of agreement, tell me that something is wrong. If I then inquire further, I may in time find the cause of error. Two or more individuals have enough of differences in their working technique that fallacies usually appear at an early stage.

Few products come from one source alone or by exclusively one procedure. There are many techniques of handling, storage and distribution, so that experience resides in an industry, rather than an individual. The people who are obliged to make use of standards have the greatest stake in their development. Making use of standards implies being governed by and governing. Successful scientific standards are almost invariably arrived at by democratic processes of trial and criticism.

The public and the pharmaceutical industry and profession have profited from the long existence of the United States Pharmacopœia and National Formulary as compendiums of quality standards, and from their recognition in the old Food and Drug and the present Food, Drug, and Cosmetics Acts. My other experience with commodity standards has been in connection with foods and textiles. Although we have excellent food standards, some of which have been almost as long in the making as drug standards, and we are beginning to make an impress with some textile standards, these two industries, which reach the consumer just as pharmacy does, would be in a far happier position today if their use standards had been produced as ours have been, and set forth in compendia of the same type.

I would close with a word of personal appreciation. I was, frankly, astonished when in 1930 I found myself a member of the U. S. P. Revision Committee. Thanks to you gentlemen, my work has been largely editorial. The excellence of our drug standards is owed to the men of the laboratories, represented by the Combined Contact Committee, and not to those who put them in pharmacopœial language. It is you who have made our work easy and precise.

# Adsorption Studies of Aureomycin Hydrochloride on Aluminum Hydroxide Gel*

By FRANK E. DI GANGI† and CHARLES H. ROGERS‡

**Aluminum hydroxide gel is quite frequently administered with aureomycin hydrochloride to counteract the nausea and vomiting in patients who cannot otherwise tolerate the antibiotic orally. *In vivo* and *in vitro* studies showed that nearly all of the activity of the antibiotic is removed through adsorption onto the aluminum hydroxide. Solutions of aureomycin hydrochloride of 1 mg. per ml. concentrations are stable for at least eight weeks if kept refrigerated. Colorimetric determinations of aureomycin hydrochloride can be performed with a Fisher Electrophotometer.**

DURING clinical investigations on the new antibiotic, aureomycin hydrochloride, Schoenbach, *et al.* (1), found that oral doses of the drug were associated with loss of appetite, nausea, and vomiting in some patients following the administration of the morning dose. These patients were completely relieved when aluminum hydroxide gel was administered with the drug (1/2 ounce per 100 mg.).

Several hospitals found that this treatment worked well with those patients who could not tolerate the drug when administered orally and therefore are still using this method of treatment routinely.

The adsorptive properties of aluminum hydroxide are well known. It was felt that with the administration of aluminum hydroxide gel, there might be some loss of activity of the aureomycin through its being adsorbed onto the particles of aluminum hydroxide.

A cursory examination of this adsorption effect was carried out in the following manner. Aluminum hydroxide gel was added to a solution of aureomycin hydrochloride and agitated frequently for one hour. The suspension was allowed to settle. The golden-colored solution of aureomycin was rendered colorless and the settled gel had assumed a bright golden color. When a portion of the suspension was alkalized to a *p*H of 8 with dilute sodium hydroxide, the color of the gel was only further intensified. Another portion of the suspension was acidified to a *p*H of 5 with dilute hydrochloric acid, which in turn completely dissolved the aluminum hydroxide and resulted in yellow-colored solution of greater intensity than the original solution of aureomycin hydrochloride.

From the above results it was assumed that the aureomycin was adsorbed onto the aluminum hydroxide and that it probably remained adsorbed and might be excreted in that form.

When this investigation was started there had been no correlation between the golden color and the activity of aureomycin. The only means of determining activity was through the use of bacteriological assays. Attempts to correlate color intensity to activity were unsuccessful since the color of the product as it appeared on the market was not constant. Since then, Levine, Garlock, and Fischbach (2) showed that the antibiotic develops a characteristic adsorption maximum in the visible portion of the spectrum after being treated with a mineral acid. The peak of absorption occurred at 440 mμ. The rate of color development is dependent upon temperature and acid concentration. Their method of colorimetric determination was then used in this work with the exception that a Fisher Electrophotometer was employed with a filter cell having a spectral band of approximately 425 mμ.

## EXPERIMENTAL

Using the method of Levine, Garlock, and Fischbach (2), a standard curve showing the relation of aureomycin concentration to the logarithmic scale reading was prepared using pure crystalline aureomycin hydrochloride and a Fisher Electrophotometer. Figure 1 is the curve prepared according to this method.

**Adsorption Studies.**—Solutions of approximately 1 mg./ml. concentrations were prepared from parenteral and capsular preparations of aureomycin hydrochloride. The 250-mg. capsules were dissolved in 250 ml. of distilled water and the 100-mg. parenteral preparation was dissolved in 100 ml. of distilled water. Fifty-milliliter portions of these solutions were added to 5.0 ml. of aluminum hydroxide gel and the resulting suspensions were then agitated for one hour at the end of which time they were centrifuged. The clear, supernatant liquid

* Received October 31, 1949, from the College of Pharmacy, University of Minnesota.
† Assistant Professor in Pharmaceutical Chemistry.
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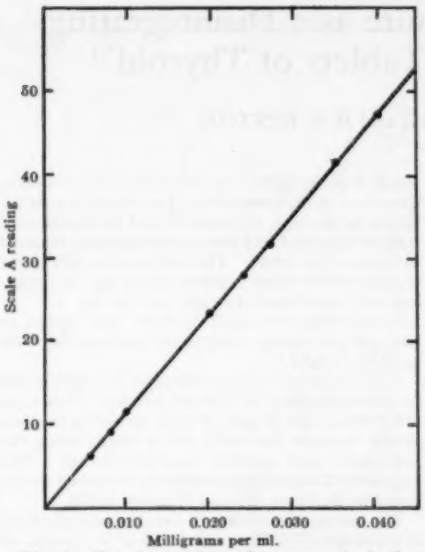


Fig. 1.—Standard curve of aureomycin hydrochloride using a Fisher Electrophotometer with filter 425-B.

was poured off. Colorimetric determinations were performed on the treated and untreated solutions of aureomycin as well as bacteriological assays to correlate color concentration to biological activity. The bacteriological assay method was that of Dornbush and Pelcak (3, 4), with a slight modification. The results are tabulated in Table I.

TABLE I.—ASSAY IN MILLIGRAMS PER MILLILITER

| Sample | Colorimetric | Bacteriological |
|---|---|---|
| Parenteral | 1.10 | 1.0 |
| | | 1.0[b] |
| Parenteral treated | 0.0011[a] | 0.00256 |
| | | 0.0[b] |
| Capsules | 1.150 | 1.00 |
| | | 1.00[b] |
| Capsules treated | 0.0[a] | 0.00512 |
| | | 0.000156[b] |
| Parenteral | 1.025 | 1.0 |
| Parenteral treated | 0.00065[a] | 0.000312 |
| Capsules | 1.150 | 1.0 |
| Capsules treated | 0.0[a] | 0.000312 |

[a] Five times the quantity was used for assay to increase the concentration per sample.
[b] Assayed after two weeks' standing.

The prepared solutions of aureomycin treated with aluminum hydroxide gel and untreated were assayed colorimetrically and bacteriologically within two hours of their preparation. However, on reassaying the solutions after two weeks' standing in the refrigerator, it was evident that no loss in biological activity occurred. The aluminum hydroxide-treated solutions were of such weak concentrations that the assay procedure was modified to the extent that 10 ml. was used in the colorimetric determinations and still the concentrations of aureomycin were well below the limits set by Levine, Garlock, and Fischbach (2).

## SUMMARY

Aluminum hydroxide gel in concentrations of 5 ml. to 50 ml. of solution of aureomycin hydrochloride (1 mg./ml.) was capable of adsorbing almost 100 per cent of the antibiotic when assayed bacteriologically and colorimetrically. The discrepancies between the two assay methods on the treated solutions in part were due to the fact that when the concentrations of the drug reached below 20 μg./ml. it did not follow the Lambert-Beer law.

In conjunction with this work Waisbren and Hueckel (4) found an identical picture when determining blood levels on patients who were administered the drug orally with aluminum hydroxide gel.

Solutions of aureomycin hydrochloride are stable for as much as eight weeks when refrigerated, provided the concentration is about 1 mg./ml., whereas solutions of weaker concentrations slowly lose some of their activity.

Colorimetric determinations of aureomycin hydrochloride can be performed using a Fisher Electrophotometer with a filter cell having a spectral band of approximately 425 mμ.

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(3) Dornbush, A. C., and Pelcak, E. J., *Ann. N. Y. Acad. Sci.*, **51**, 218(1948).
(4) Waisbren, B. A., and Hueckel, J. To be published in *Proc. Soc. Exptl. Biol. Med.*, a note to the editor of *J. Am. Med. Assoc.*

## CORRECTION

In the article entitled "Studies on Sex Variation to Picrotoxin in the Albino Rat" by Harald G. O. Holck [THIS JOURNAL, **38**, 604–610 (November, 1949)] the word "corticosterone" should be changed to read "desoxycorticosterone." The incorrect designation appears in five places as follows: on page 609, in the ninth line of the first paragraph, in the tenth line of the second paragraph, and in Table XIII; on page 610 at the end of the second complete paragraph and in the tenth paragraph of the summary.

# The Use of Dried Bentonite as a Disintegrating Agent in Compressed Tablets of Thyroid*,†

By C. BOYD GRANBERG and B. E. BENTON

**The results of the use of dried bentonite as the disintegrating agent in compressed tablets of thyroid are reported. Methods of determining the degree of hardness and relative rate of disintegration are included.**

THE employment of a disintegrant in the manufacture of compressed tablets was one of the most important discoveries in this field. It allowed the compression of insoluble and slightly soluble as well as soluble drugs.

A disintegrating agent may be defined as a substance which is added to a tablet granulation to insure the breaking up of the tablet after it is swallowed.

The disintegrating agents most commonly employed are corn starch or potato starch. These substances have a great affinity for water (1) and in their rapid absorption of water the starch grains swell to many times their normal size, thus rupturing the tablet or granule.

This paper attempts to open the way to the use of bentonite as a disintegrating agent. Thyroid tablets were chosen for this investigation for two reasons. First, because the color of bentonite is approximately the same as the color of powdered thyroid, there could be no objection to a discoloration of the tablets as would have been possible if a white powder had been chosen. Secondly, the previous formula for thyroid tablets compiled by the University of Illinois College of Pharmacy Manufacturing Laboratory contained no disintegrating agent, and a study of both starch and bentonite as a disintegrant in this tablet could be conducted at the same time.

## EXPERIMENTAL

In considering the tablets manufactured for this problem, particular attention was paid to the appearance of the tablet and the degree of hardness, as well as to the relative disintegration time.

Judgment of the appearance of the tablets was based on whether the surface of the tablet was smooth or mottled, and whether the edges were complete and firm or chipped and soft.

The degree of hardness was measured by an instrument known as a Hardness Tester for Tablets which was furnished by the Monsanto Chemical Company of St. Louis, Mo. The instrument is designed to permit a determination of the hardness of tablets expressed in kilograms of pressure required to fracture the tablet. The scale on the instrument is graduated to allow readings of 0.5 Kg., but readings may be estimated readily to 0.25 Kg.

Ten tablets from each formula were tested to produce an average degree of hardness or "dry breaking weight."

The relative rate of disintegration was determined by measuring the "wet breaking time." This term is defined as the length of time necessary to completely fracture the tablet being tested using the instrument and method described below. The apparatus is a modification of one described in the literature by Berry (2), and is shown in Fig. 1.

The instrument consists of a rectangular platform of stainless steel with an aperture $^1/_8$ by $^7/_8$ inch. A stainless steel cutting shaft with a weight of ball-bearing steel is affixed with $^1/_8$ inch guiding shafts to this rectangular platform. A knife blade $^1/_{16}$ by $^3/_4$ inch is silver-soldered to the weighted shaft in a manner that will allow the blade to fall into the aperture. A weight of 20 Gm. was chosen for the weight of the cutting shaft because it was not sufficiently heavy to cause a dry break of the tablets and yet was heavy enough not to be held up by the softened tablet mass.

The method used for obtaining the relative rate of disintegration is as follows: A solution simulating gastric juice was prepared according to the following formula (3).

Acid-Pepsin Solution
pH—1.7
Sp. gr.—1.0024

| | | |
|---|---|---|
| Sodium Chloride | 1.4 | Gm. |
| Potassium Chloride | 0.5 | Gm. |
| Calcium Chloride | 0.06 | Gm. |
| Hydrochloric Acid (36%) | 6.944 | Gm. |
| Pepsin (U. S. P.) | 3.2 | Gm. |
| Distilled Water, *q. s. ad.* | 1000.0 | cc. |

A 2-L. flask containing the acid-pepsin solution was placed in a constant-temperature water bath. The tablet being tested was centered over the aperture of the rectangular platform, and the blade of the weighted shaft allowed to rest on the center of the tablet. The entire arrangement was placed on the 2-L. flask so that the tablet was submerged about $^1/_4$ inch below the surface of the acid-pepsin solution. As the tablet softened, the blade of the weighted shaft cut through it and ultimately fell through the aperture. The fall was quick and well defined, therefore a sharp end point was easily discernible. The acid-pepsin solution was gently stirred at frequent intervals to bring fresh solution to the tablet and to remove those particles breaking off the disintegrating tablet.

Ten tablets from each formula were tested to give an average wet breaking time expressed in minutes and seconds.

* From the University of Illinois College of Pharmacy Manufacturing Laboratory, Chicago, Ill.
Presented to the Scientific Section, A. PH. A., San Francisco meeting, August, 1948.
† Abstract of thesis submitted by C. Boyd Granberg in partial fulfillment of the requirements for the degree of Master of Science in Pharmacy in the Graduate School of the University of Illinois, 1947.

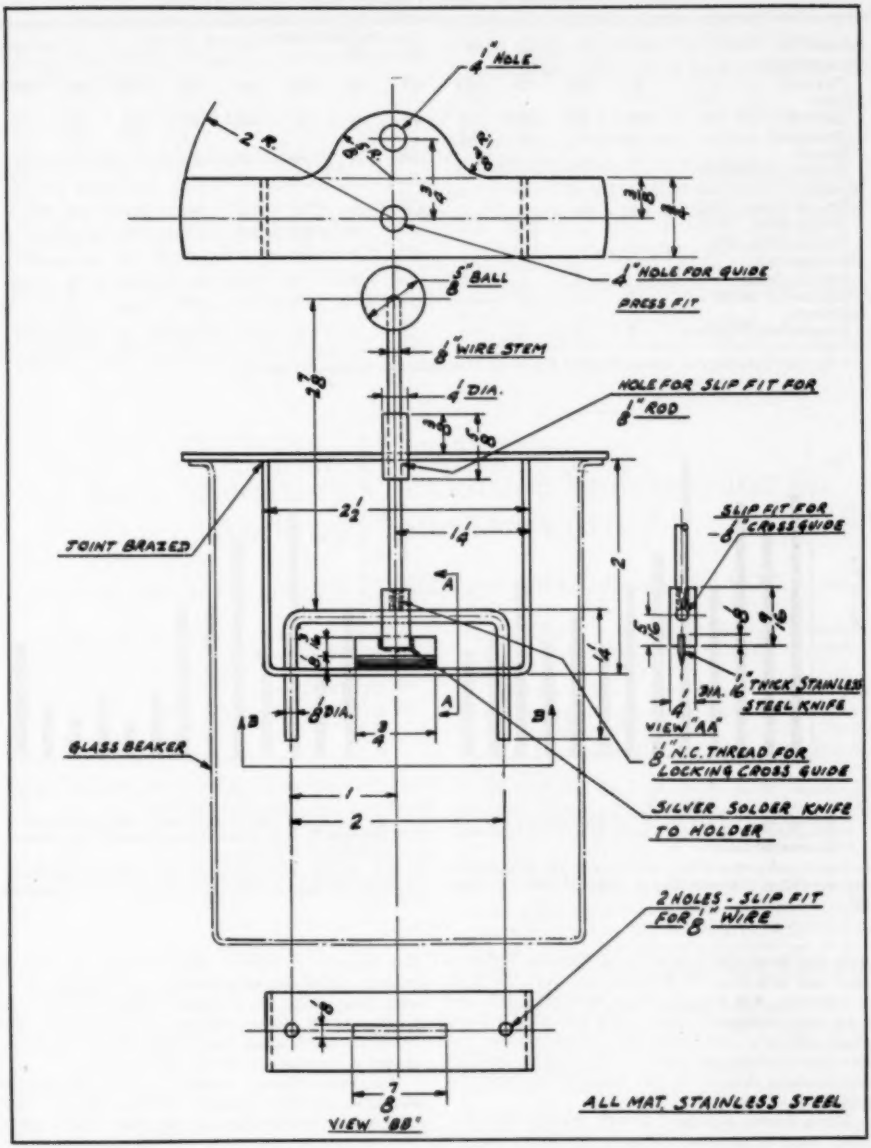



Fig. 1. Drawing plan of instrument used to determine wet breaking time.

In the trial formulas investigated, dried starch and dried bentonite were compared as disintegrants. In addition, bentonite, starch, lactose, and powdered sucrose were used as fillers in varying combinations and quantities. The binding solutions employed were 15% starch paste, 10% acacia solution, and a 4% acacia solution. Magnesium stearate was used in all formulas as the lubricating agent. Table I represents the formulas tested.

The appearance of the tablets produced from all the trial formulas compared very favorably with any thyroid tablet observed on the market.

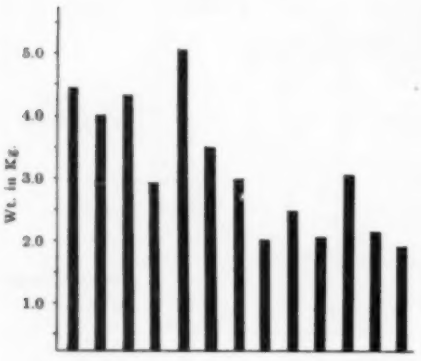
There was, however, considerable variation noted in the average dry breaking weights and the average wet breaking times of the various formulas. These variations are set forth in Figs. 2 and 3.

The tablets from Formula No. 9 proved to be the most satisfactory in all respects. It is interesting to

TABLE I.—FORMULAS OF 65-MG. THYROID TABLETS INVESTIGATED

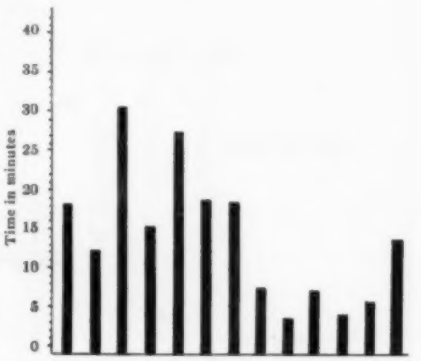
| Formula No. | Mg. per Tablet | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12[a] |
| Medicament: | | | | | | | | | | | | |
| Thyroid | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 |
| Fillers: | | | | | | | | | | | | |
| Lactose | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 35 | 35 | 35 | 35 |
| Bentonite | 10 | 10 | 10 | 10 | .. | .. | .. | .. | 10 | 10 | 10 | .. |
| Starch | .. | .. | .. | .. | 10 | 10 | 10 | 10 | .. | .. | .. | 12 |
| Sucrose, powdered | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | 10 |
| Binders: | | | | | | | | | | | | |
| Starch Paste, 15% | *q.s.* | *q.s.* | .. | .. | *q.s.* | *q.s.* | .. | .. | *q.s.* | *q.s.* | *q.s.* | .. |
| Acacia Soln., 10% | .. | .. | *q.s.* | *q.s.* | .. | .. | *q.s.* | *q.s.* | .. | .. | .. | .. |
| Acacia Soln., 4% | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | *q.s.* |
| Disintegrants: | | | | | | | | | | | | |
| Starch, dried | .. | 6 | .. | 6 | .. | 6 | .. | 6 | .. | 12 | 6 | 0 |
| Bentonite, dried | 6 | .. | 6 | .. | 6 | .. | 6 | .. | 12 | .. | 6 | 0 |
| Lubricant: | | | | | | | | | | | | |
| Magnesium Stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 |

[a] Previous University of Illinois Hospital Pharmacy Manufacturing Laboratory formula.




[a] Average figure of five lots of tablets from this formula.
[b] Previous U. of Ill. Hosp. Pharm. Manuf. Lab. formula.
[c] Commercial tablet.

Fig. 2.—A comparison of the average dry breaking weight of thirteen 65-mg. thyroid tablet formulas.




[a] Average figure of five lots of tablets from this formula.
[b] Previous U. of Ill. Hosp. Pharm. Manuf. Lab. formula.
[c] Commercial tablet.

Fig. 3.—A comparison of the average wet breaking time of thirteen 65-mg. thyroid tablet formulas.

note that bentonite is used in this formula both as a filler and (dried) as the disintegrant. As a check on the formula, five lots of tablets were prepared, and each trial produced tablets with the same general characteristics. Dry breaking weights from the five lots of tablets averaged 2.5 Kg., and the average wet breaking time of the five lots was three minutes and forty-two seconds.

These figures represent a very definite improvement over a previous formula developed at the University of Illinois. Tablets from this formula presented an average dry breaking weight of 3.075 Kg., and an average wet breaking time of seventeen minutes and seventeen seconds. The figures of tablets from Formula No. 9 also compare very favorably with a commercial 65-mg. thyroid tablet which had an average dry breaking weight of 1.90 Kg., and was found to have an average wet breaking time of thirteen minutes and forty-six seconds.

To determine the effect of bentonite on the liberation of iodine from its combination with thyroid, five samples of thyroid tablets from two lots of tablets manufactured according to Formula No. 9 were assayed by the Chemistry Department of the University of Illinois College of Pharmacy. The U. S. P. XIII assay for thyroid tablets was employed. Results are shown in Table II.

These data plainly indicate that chemically the liberation of iodine from its combination with thyroid is not hindered by the presence of bentonite.

TABLE II.—EFFECT OF BENTONITE ON THE ASSAY OF THYROID TABLETS

| Assay No. | Amount of Iodine per Tablet, Mg. | Iodine of the Labeled Amount of Thyroid, % |
|---|---|---|
| 1 | 0.14 | 0.21 |
| 2 | 0.13 | 0.20 |
| 3 | 0.13 | 0.20 |
| 4 | 0.13 | 0.20 |
| 5 | 0.12 | 0.19 |

Clinically, over 2,500,000 thyroid tablets manufactured from Formula No. 9 have been used in the University of Illinois Hospitals and dispensed through the hospital pharmacy with completely satisfactory results.

## SUMMARY

Twelve trial formulas for 65-mg. thyroid tablets are presented. Dried starch and dried bentonite are compared as disintegrants. The dry breaking weights and wet breaking times of the 12 formulas are plotted in comparison with the values of a commercial tablet and the formula previously used at the University of Illinois Manufacturing Pharmacy Laboratory.

A formula for 65-mg. thyroid tablets containing bentonite as a filler and a disintegrant is presented as having been produced with good results at the University of Illinois Manufacturing Pharmacy Laboratory on a semicommercial scale.

A device for measuring the relative disintegration time of compressed tablets is described, and working plans of its construction are given in detail. The method for determining the relative disintegration time is thoroughly discussed.

## REFERENCES

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# A New Microchemical Outside Indicator for the Anthraquinone Derivatives*,†

By BERNARD V. CHRISTENSEN‡ and ISMAIL A. ABDEL-LATIF§

**The red color developed by the alkalies with the anthraquinone derivatives is used as an outside indicator for their detection in any solution or extract. The test is extremely sensitive and the colors obtained are quite stable.**

THE USE OF solid potassium hydroxide or other solid alkalies as an outside indicator was tried as a means for the detection of the presence or absence of anthraquinone derivatives in any solution or extract, whatever the solvent might be.

## EXPERIMENTAL

**Procedure.**—A drop of the extract to be tested was taken out and added to a pellet of pure potassium hydroxide on a spot plate. A red color developed immediately if any trace of the anthraquinone derivatives existed. Results were always checked with blanks and control experiments.

In cases where solutions in organic solvents were tested, the color developed in a few seconds after the organic solvent volatilized. The color developed faster with ether than with chloroform and very slowly in case of amyl alcohol.

In the case of slowly evaporating organic solvents, it was found advantageous to warm the solution on the spot plate, on a steam bath, then add a drop of water to the residue, followed by a pellet of potassium hydroxide.

The test was also successful using sodium hydroxide pellets, borax, and sodium bicarbonate. Potassium and sodium hydroxides gave much better results than the other alkalies, which in some instances did not develop the color until a drop of water was added. This may be explained by the fact that the caustic alkalies are deliquescent.

**Sensitivity.**—The test is sensitive to dilutions as high as 0.00002 Gm. senna extractive per drop of extract, or at least to $^1/_{500,000}$ dilution of anthraquinone derivatives.

**Advantages of the Outside Indicator.**—The advantages of this indicator are: (*a*) applicability to all types of solutions or extracts of the anthraquinone derivatives regardless of the solvent; (*b*) time- and equipment-saving; (*c*) usefulness in quantitative extractions of emodin-containing drugs; (*d*) it is extremely sensitive and specific; and (*e*) the colors as well as the fluorescence are stable for at least twenty-four hours.

## SUMMARY

Potassium hydroxide pellets are recommended to be used as an outside indicator for the detection of traces of anthraquinone derivatives in any extract of the emodin drugs or as a solution thereof, whatever the solvent may be.

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* Received April 4, 1949, from the Pharmacognosy Research Laboratory, College of Pharmacy, The Ohio State University, Columbus, Ohio.
Presented to the Scientific Section, A. PH. A., Jacksonville meeting, April, 1949.
† Abstract of dissertation submitted to the Graduate School by I. A. Abdel-Latif in partial fulfillment of the requirements for the degree of Doctor of Philosophy.
‡ Dean of the College of Pharmacy, The Ohio State University.
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# A New Fluorometric Method of Assay for Alexandria Senna Leaves (*Cassia Acutifolia,* Delile)*,†

By BERNARD V. CHRISTENSEN‡ and ISMAIL A. ABDEL-LATIF§

**The logarithms of the percent fluorescences vary inversely with the relative concentrations of ammonia layers obtained when different weights or samples of Alexandria senna leaves are subjected to Borntraeger's reaction under specific conditions. The method of assay is sensitive, accurate, and rapid. It should be used comparatively until a reference standard is established.**

IN A PRECEDING paper (1), the authors have shown that the pink fluorescence of certain extracts is evidently due to the anthraquinone derivatives in senna.

The degree or intensity of fluorescence varies inversely with the extent of transmission or the depth of penetration of the stimulating light, which depends on the concentration of the solution. Consequently, the human eye judgment of the degree of fluorescence will be, in most cases, in reverse order to the actual quantity of re-emitted fluorescence. However the use of the new microtechnique with capillary tubes (2) will in part correct this factor of penetration and absorption of the incident light since there will be no significant depth of the solution or sample to allow for any appreciable difference in the absorption. Using the capillary tube method the degree of fluorescence was found to vary with the concentration of the anthraquinone derivatives present in the prepared quantitative dilutions.

This phenomenon suggested the use of accurate fluorometers to determine the exact relationship between fluorescence and concentration.

## EXPERIMENTAL

### The Fluorometer

The "Lumetron" (3) was used in all the fluorometric determinations in this work. Figure 1 shows the principle of operation of the Lumetron.

In the present work it was found that the reduction plate No. 2 was the most satisfactory type to be inserted in the path of the incident balancing beam.

The following filters were found suitable in carrying the fluorometric measurements of the ammonia layers when senna was extracted:

**Primary Filter.**—The so-called "Vitamin A primary," furnished with the Lumetron.

**Secondary Filter.**—A set of two pairs, one pair is placed on each side of the sample holder.

*a. Porphyrin Secondary.*—Red filter placed toward sample holder.

*b. Vitamin $B_2$ Secondary.*—Dark yellow filter placed toward the photocell.

These filters[1] are given the above names by the manufacturer due to their common use in the determination of the respective vitamins.

### Procedure

The same procedure outlined in a previous paper (4) was followed in the preparation of an ether extract of senna leaves each cc. of which represents the extractive from 8 mg. senna. The ether extract was shaken with ammonia T. S. and the ammonia layer separated by centrifuge.

Various dilutions of the ammonia layer were quantitatively prepared using Ammonia T. S. to complete each volume up to 25 cc. Ammonia T. S. (previously shaken with pure ether) was used as a blank.

The fluorescences of the ammonia layers were measured with the Lumetron. The fluorescence (%) varied *inversely* with the relative concentration. The logarithms of the % fluorescence vary indirectly and quantitatively with the relative concentration. Table I summarizes the results obtained. Figures 2 and 3 illustrate the linear indirect relationship between the logarithm of the % fluorescences and the relative concentrations. Consequently, fluorescence may also be used as a basis for a method of assay for senna.

The unknown concentrations can be found from the graph of at least two knowns. By determining the % fluorescence of the unknown and its logarithm, the concentration can be determined.

Another method is the use of the mathematical equation (see next page):

* Received April 4, 1949, from the Pharmacognosy Research Laboratory, College of Pharmacy, the Ohio State University, Columbus.

Presented to the Scientific Section, A. PH. A., Jacksonville Meeting, April, 1949.

† Abstract of dissertation submitted to the graduate school by I. A. Abdel-Latif in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

‡ Dean of the College of Pharmacy, The Ohio State University.

§ Former lecturer, Pharmacognosy Dept., College of Pharmacy, Fouad I Univ., Cairo, Egypt. Former instructor of Pharmacognosy, College of Pharmacy, The Ohio State University.

[1] The primary glass filter called "Vitamin A primary" is, in fact, a component of the Vitamin A filter combination supplied. It is the "Corning" glass #5840 which transmits from 310 to 390 and has its peak at 360 mμ. Therefore, the exciting light obtained was in the wave band from 310 to 390 mμ. With the mercury vapor lamp almost all of the energy was in the 365 mμ line and some little energy in the 334 mμ line. The fluorescence excited by the above-described energy was filtered by the combination of secondary filters used in the following manner. The fluorescence light will pass first through the red porphyrin filters. These transmit only radiation of wave length longer than about 600 mμ. The fluorescence light then passes through the dark yellow glass filter (Vitamin $B_2$ secondary) but this does not absorb any of the red radiation except that it cuts it down about 15%. The secondary filter for Vitamin $B_2$ is the Corning glass #3486 which absorbs all the radiation below 520 and transmits freely above 520 mμ.

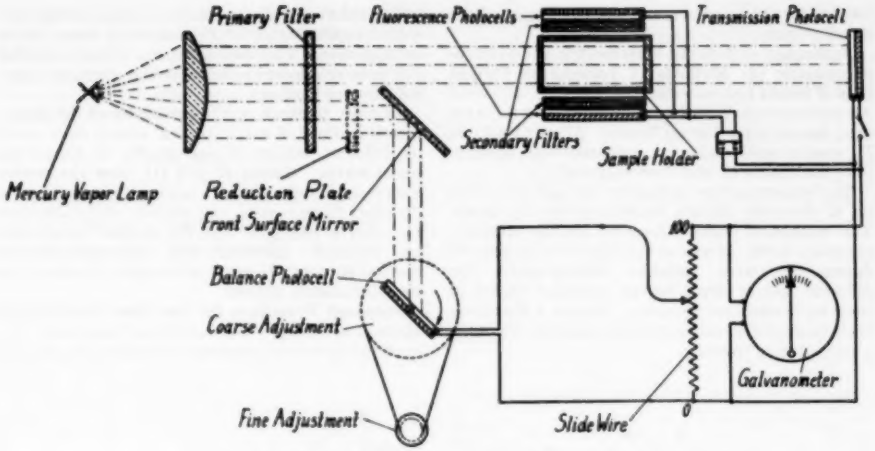


Fig. 1.—The lumetron, principle of operation.

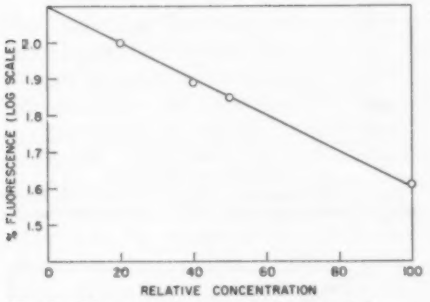


Fig. 2.—Fluorometric analysis of ammonia layers.

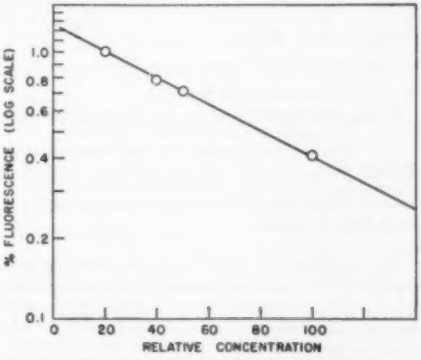


Fig. 3.—Fluorometric analysis of ammonia layers.

$$\text{Slope} = \frac{F - F_1}{C - C_1} = \frac{F_2 - F_1}{C_2 - C_1}$$

where

$F$ = logarithm fluorescence of unknown (determined experimentally)
$C$ = concentration of unknown
$F_1$ and $F_2$ = logarithm fluorescence of the two knowns
$C_1$ and $C_2$ = concentrations of the two knowns, respectively

Using this equation, the error was found to vary between 2 and 7% which is quite satisfactory with the dilutions used (each cc. of ammonia layer represented the extractive from 8 mg. senna).

Considering the negligible error, especially when milligrams of a crude drug are used, the fluorometric measurements of the ammonia layer are very accurate and sensitive. They can be used as a basis for a

TABLE I.—FLUOROMETRIC ANALYSIS OF QUANTITATIVE DILUTIONS OF THE AMMONIA LAYER

| Expt. No. | Ammonia Layer Taken, Cc.[a] | Ammonia T. S. Added, Cc. | Total Volume Obtained, Cc. | Fluorescence (Dial Readings), % | Log, % Fluorescence ($F$),[b] | Relative Concentration, % — Prepared ($C$)[c] | Found | Error |
|---|---|---|---|---|---|---|---|---|
| I | 25 | 0.0 | 25 | 40.75 | 1.6101 | 100 | 100.000 | Control |
| II | 12.5 | 12.5 | 25 | 70.5 | 1.8482 | 50 | 51.146 | 2.292 |
| III | 10 | 15 | 25 | 78 | 1.8921 | 40 | 42.395 | 6.987 |
| IV | 5 | 20 | 25 | 100 | 2.0000 | 20 | 20.000 | Control |
| Blank | 0.0 | 25 | 25 | 0.0 | $-\infty$ | 0.0 | 0.0 | ... |

[a] Each cc. of the "Ammonia Layer" represents the extractive from 8 mg. senna.
[b] ($F$) symbol for the figures in the respective column, in the algebraic equations used.
[c] ($C$) represents the figures in the respective column in the algebraic equations used.

method for the assay of senna and possibly of all the emodin drugs.

**Application of Both the Fluorometric and Spectrophotometric (4) Methods of Analysis to Various Lots of Senna Leaves.**—Six different U. S. P. lots of Alexandria senna leaves were obtained from different drug houses in the United States. All met the U. S. P. requirements and were analyzed both spectrophotometrically (4) and fluorometrically.

The concentrations prepared were such that each cc. of the ether extract represented 10 mg. senna. The extinction values obtained for the different ammonia layers, as well as the logarithms of their % fluorescence were variable. Consequently, the different lots of senna leaves examined varied in their anthraquinone contents. Figure 4 illustrates both fluorometric and spectrophotometric results in a comparative manner.

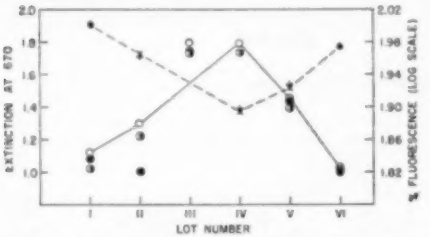


Fig. 4.—Spectrophotometic and fluorometric comparison of various lots of senna.
—— Spectrophotometry: ○, read immediately; ◑, read after 12 hours; ●, ether layer allowed to stand two days, then shaken with ammonia T.S.
– – – Fluorometry: ×, read immediately; +, read after 16 hours.

The fluorometric analysis of the ammonia layer confirmed the spectrophotometric method and vice versa. The extinction values varied *directly* while the log % fluorescence varied *inversely* with the relative concentrations of the anthraquinones present.

TABLE II.—FLUOROMETRIC ASSAY OF VARIOUS QUANTITIES OF SENNA

| Expt. No. | Weight of Senna Gm. | Log. % Fluorescence, | Relative Concentration, % Prepared | Found[a] | Error |
|---|---|---|---|---|---|
| I | 9.5 | 1.9101 | 95 | 95.000 | Control |
| II | 9.0 | 1.9138 | 90 | 93.971 | 4.41 |
| III | 8.5 | 1.9542 | 85 | 82.587 | 4.22 |
| IV | 8.0 | 1.9557 | 80 | 82.313 | 2.89 |
| V | 7.0 | 2.0000 | 70 | 70.000 | Control |

[a] Calculated by the mathematic equation for the slope.

The colors and fluorescences of the ammonia layers were quite stable for at least thirty hours under refrigeration. The measurements always showed the same relationship irrespective of the time interval between readings.

In order to check on the sensitivity of the fluorometric method of assay, several assays were made on different weights of one sample of Alexandria senna leaves. Tables II and III show the results obtained as well as the % error. Figures 5 and 6 illustrate these results, respectively, and show that the error is negligible and the method is accurate and senstive. However, the spectrophotometric method of assay (4) seems to be more sensitive than the fluorometric method.

**Proposed Procedure for the New Fluorometric Method of Assay.**—The method of procedure outlined for the spectrophotometric method of assay (4)

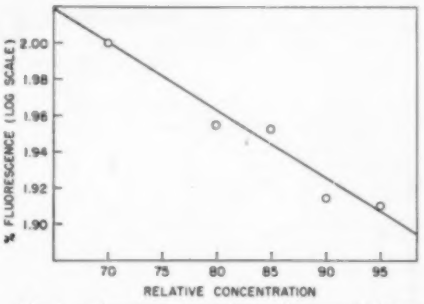


Fig. 5.—Fluorometric analysis of ammonia layers using different quantities of the same senna sample.

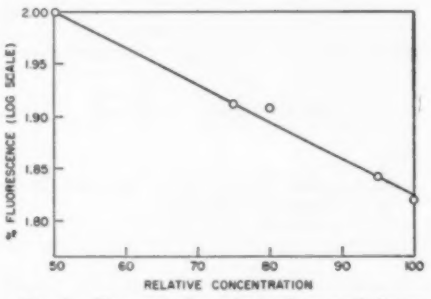


Fig. 6.—Fluorometric analysis of ammonia layers using different quantities of the same sample of senna.

TABLE III.—FLUOROMETRIC MEASUREMENTS OF THE AMMONIA LAYERS OBTAINED WITH DIFFERENT QUANTITIES OF SENNA

| Expt. No. | Weight of Senna, Gm. | Fluorescence, % | Log. % Fluorescence | Relative Concentration, % Prepared | Found[a] | Error |
|---|---|---|---|---|---|---|
| I | 10.00 | 65.2 | 1.8136 | 100 | 100 | Control |
| II | 10.0 | 66.3 | 1.8215 | 100 | 97.827 | 2.173 |
| III | 9.5 | 69.8 | 1.8439 | 95 | 91.872 | 3.292 |
| IV | 8.0 | 81.2 | 1.9096 | 80 | 74.249 | 7.176 |
| V | 7.5 | 82.0 | 1.9138 | 75 | 73.123 | 2.502 |
| VI | 5.0 | 100 | 2.0000 | 50 | 50 | Control |

[a] Calculated using the slope equation.

is to be followed exactly for this fluorometric method, except that the volume of the ammonia layer necessary for fluorometric measurements is usually as large as 25 cc., which makes it necessary to shake at least 80 cc. of the ether extract with 30 cc. of freshly prepared Ammonia T. S.

## SUMMARY

A new fluorometric method of assay for the anthraquinone constituents in the Alexandria senna leaves has been devised. The method is rapid, accurate, and sensitive. The procedure is comparative until a reference standard is established for senna leaves. It is probable that the method may be applicable to other emodin drugs.

## REFERENCES

(1) Christensen, B. V., and Abdel-Latif, I. A., THIS JOURNAL, **38**, 487(1949).
(2) Christensen, B. V., and Abdel-Latif, I. A., THIS JOURNAL, **38**, 490(1949).
(3) "Lumetron" Photo-Electric Fluorometer Model 402 EF, Photovolt Corporation, 95 Madison Ave., New York 16, N. Y.
(4) Christensen, B. V., and Abdel-Latif, I. A., THIS JOURNAL, **38**, 589(1949).

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# 1950 Iodine Research Award Nominations Requested

Nominations are now being received by the AMERICAN PHARMACEUTICAL ASSOCIATION for the 1950 Iodine Educational Bureau Award recognizing outstanding research in the chemistry and pharmacy of iodine and its compounds as applied in pharmacy or medicine. Any member of the ASSOCIATION may propose a nominee by submitting eight copies of each of the publications to be considered in the competition, a biographical sketch of the nominee including date of birth, and a list of his publications. Eight copies of the nomination must be submitted to Robert P. Fischelis, Secretary of the AMERICAN PHARMACEUTICAL ASSOCIATION, 2215 Constitution Ave., N. W., Washington 7, D. C. To be eligible for the 1950 Award, nominations must be received on or before January 1, 1950.

A nominee must be a resident of the United States or Canada. He must have accomplished outstanding research in the chemistry or pharmacy of iodine and its compounds as applied in pharmacy or medicine.

During the period covered by the nomination the nominee shall have been actively engaged in, shall have completed, or shall have published a report upon the line of investigation for which the award is made. During a period of two years prior to the date of nomination, the nominee shall not have been engaged in research under the sponsorship of the Iodine Educational Bureau, Inc.

The award consists of $1000 and a diploma setting forth the reasons for selection of the recipient. It may be presented annually at the annual meeting of the AMERICAN PHARMACEUTICAL ASSOCIATION.

The recipient will deliver a paper or lecture upon the subject of his scientific work at the meeting at which the award is conferred. His paper, or address, will then be published in the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION. In addition to the sum of the award, the recipient will receive an allowance of not more than $250 to defray his expenses in attending the meeting.

The recipient will be selected by an award committee which is appointed by the chairman of the ASSOCIATION'S Council and which functions under prescribed rules. The present committee includes Justin L. Powers, chairman; Louis Gershenfeld, Charles O. Wilson, Harvey B. Haag, Heber W. Youngken, John C. Krantz, and Frank O. Taylor.

The award is now in its third year. The recipient of the first award was Dr. William T. Salter, Yale University pharmacologist. Dr. George M. Curtis, Chairman of the Department of Surgical Research and Professor of Surgery at Ohio State University, will be the recipient of the second award and will give the 1950 Iodine Award lecture.

# United States Pharmacopœial Convention

## *Ninth Annual Financial Statement, Covering the Period from May 1, 1948 to April 30, 1949, and Based Upon the Report of the Auditor*

### STATEMENT OF INCOME AND EXPENSE

| | | | | |
|---|---|---|---|---|
| INCOME | | | | |
| Sale of Pharmacopœias: | | | | |
| Collections | | | $82,979.23 | |
| Less: Decrease in Accounts Receivable: | | | | |
| April 30, 1948 | | $20,609.74 | | |
| April 30, 1949 | | 7,163.92 | 13,445.82 | $69,533.41 |
| Sale of Reference Standards, A. M. A. articles, etc.: | | | | |
| Collections | | | $13,139.70 | |
| Less: Decrease in Accounts Receivable: | | | | |
| April 30, 1948 | | $ 1,787.20 | | |
| April 30, 1949 | | 1,748.50 | 38.70 | |
| | | | $13,101.00 | |
| Add: Increase in Collections Pending Remittance to Treasurer: | | | | |
| April 30, 1949 | | $ 725.75 | | |
| April 30, 1948 | | 696.75 | 29.00 | 13,130.00 |
| Interest on Investments: | | | | |
| Collections | | | $ 6,350.00 | |
| Less: Decrease in Accrued Interest Receivable: | | | | |
| April 30, 1948 | | $ 2,236.99 | | |
| April 30, 1949 | | 2,086.99 | 150.00 | |
| | | | $ 6,200.00 | |
| Less: Amortization of Bond Premiums | | | 82.09 | 6,117.91 |
| Miscellaneous Income: | | | | |
| Collections | | | | 1,125.79 |
| TOTAL INCOME | | | | $89,907.11 |
| LESS—EXPENSE: | | | | |
| Publication and Sales Expense | | $ 9,039.31 | | |
| Add: Decrease in Inventory: | | | | |
| April 30, 1948 | $14,155.07 | | | |
| April 30, 1949 | 5,571.48 | 8,583.59 | $17,622.90 | |
| Administration | | | 5,923.44 | |
| Revision | | $41,612.79 | | |
| Less: Increase in Inventory: | | | | |
| April 30, 1949 | $12,797.34 | | | |
| April 30, 1948 | 10,139.13 | 2,658.21 | 38,954.58 | |
| Research | | | 13,978.49 | |
| Convention | | | 1,628.23 | |
| Stationery and Supplies—Inventory Adjustment | | | 282.95 | |
| Provision for Depreciation: | | | | |
| Building | | $ 346.71 | | |
| Furnishings and Equipment | | 254.50 | 601.21 | 78,991.80 |
| EXCESS OF INCOME OVER EXPENSE | | | | |
| For the year ended April 30, 1949 | | | | $10,915.31 |

### STATEMENT OF CASH RECEIPTS AND DISBURSEMENTS

| | | | |
|---|---|---|---|
| CASH ON DEPOSIT, April 30, 1948 | | | $ 76,987.01 |
| ADD—RECEIPTS: | | | |
| Sale of Pharmacopœias | | $82,979.23 | |
| Sale of Reference Standards, A. M. A. Articles, etc. | | 13,139.70 | |
| U. S. Treasury Bonds—Called | | 20,000.00 | |
| Interest on Investments | | 6,350.00 | |
| Use of Text by Others | | 1,065.00 | |
| Miscellaneous | | 60.79 | 123,594.72 |
| | | | $200,581.73 |

LESS—DISBURSEMENTS:

| | Publication and Sales | Administration | Revision | Research | Convention | Total |
|---|---|---|---|---|---|---|
| Printing and binding | $9,039.31 | | | | | $ 9,039.31 |
| Salaries | | $1,700.00 | $17,483.32 | $ 9,200.00 | | 28,383.32 |
| Clerical | | 1,402.10 | 9,068.63 | 257.25 | | 10,727.98 |
| Meetings | | 1,272.08 | 3,571.75 | 2,895.21 | 1,520.06 | 9,259.10 |
| Supplies | | 92.45 | 1,124.19 | 921.97 | | 2,138.61 |
| Postage and telegrams | | 227.01 | 1,327.44 | 88.75 | 36.32 | 1,679.52 |
| Headquarters | | | 1,500.09 | | | 1,500.09 |
| General | | 1,229.80 | 7,537.37 | 615.31 | 71.85 | 9,454.33 |
| | $9,039.31 | $5,923.44 | $41,612.79 | $13,978.49 | $1,628.23 | $72,182.26 |

| | | |
|---|---|---|
| ADD: | | |
| Purchase of furnishings and equipment | 230.40 | |
| Building fund advances | 63,079.38 | |
| | | $135,492.04 |
| CASH ON DEPOSIT, April 30, 1949 | | 65,089.69 |

## A MORE DETAILED AND SUPPLEMENTARY STATEMENT OF THE REVISION AND RESEARCH EXPENSES 1948–1949

### REVISION—MEETINGS

| | | |
|---|---|---|
| CONFERENCES: | | |
| Including transportation, hotel, meals and similar expenses for Chairman Cook and others for special conferences on U. S. P. problems | $1,904.59 | |
| Similar expenses for Executive Committee meeting and Parenteral Products hearing | 1,667.16 | $3,571.75 |

### REVISION—SUPPLIES

| | | |
|---|---|---|
| Stationery | $ 443.48 | |
| Mimeograph | 418.66 | |
| Miscellaneous | 262.05 | 1,124.19 |

### REVISION—HEADQUARTERS

| | | |
|---|---|---|
| Janitor—part time | $ 826.90 | |
| Utilities, supplies, maintenance, insurance | 673.19 | 1,500.09 |

### REVISION—GENERAL

| | | |
|---|---|---|
| Reference Standards | $5,590.76 | |
| Exhibits, etc. | 1,709.49 | |
| Miscellaneous | 237.12 | 7,537.37 |

### RESEARCH

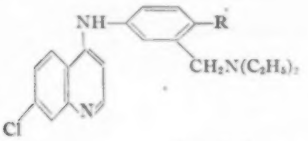
| Subcommittee | Meetings, Supplies, Postage, Clerical, Travel, General | Technical Assistance | |
|---|---|---|---|
| No. 1—Scope | 14.64 | | |
| 2—Bio Assays | 105.73 | | |
| 7—Inorganic Chemicals | 153.53 | $3,000.00 | |
| 8—Organic Chemicals | 1,014.89 | 5,600.00 | |
| 10—Volatile Oils | 105.42 | | |
| 11—Ointments | | 600.00 | |
| Amino Acids Board | 834.78 | | |
| Anti-Anemia Board | 1,082.95 | | |
| Endocrine Products Board | 587.83 | | |
| Sterile Products Board | 165.46 | | |
| Vitamin Board | 588.26 | | |
| Miscellaneous Supplies | 125.00 | | |
| | $4,778.49 | $9,200.00 | $13,978.49 |

# The Anomalous Antimalarial Activity of O-Methyl Camoquin*,†

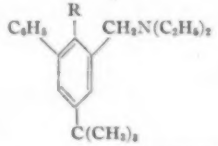
By J. H. BURCKHALTER

**The structure of O-methyl 4-(7-chloro-4-quinolylamino)-α-diethylamino-o-cresol (O-methyl Camoquin) has been confirmed, and attention has been called to its apparent anomalous antimalarial activity against trophozoite-induced *P. gallinaceum* in chicks. Certain considerations suggest that the unexpected antimalarial activity of O-methyl Camoquin may be explained through an *in vivo* demethylation to the highly effective antimalarial Camoquin.**

O-METHYL CAMOQUIN (I*b*) has been found to be as active against chick malaria as the highly potent parent Camoquin (I*a*).[1] This effectiveness is surprising since O-methylation of other active cresols has resulted in a loss of activity (2). For example, II*a* is twice as active as quinine, while its methylated derivative (II*b*) not only is devoid of activity, but it is also toxic to the host.




| I | R | Q equivalent |
|---|---|---|
| *a* | OH | 25 |
| *b* | $OCH_3$ | 25 |
| *c* | H | 1 |




| II | R | Q equivalent |
|---|---|---|
| *a* | OH | 2 |
| *b* | $OCH_3$ | 0 |

Despite the confirmatory elementary analyses of both Camoquin and O-methyl Camoquin (1), the fact that the bases melt only a few degrees apart (208° and 203°, respectively) suggests a possibility of chemical identity. Mixed melting point data, however, have now shown by a decided depression (175°–182°) that the compounds are different. Further, Zeisel methoxyl determinations (*calcd.* for $C_{21}H_{24}ClN_3O{:}CH_3O$, 8.38; found: $CH_3O$, 8.26) have confirmed the structure assigned to O-methyl Camoquin. These data appear conclusively to eliminate the possibility that the drug had been demethylated by an acidic medium during its preparation (1).

A possible explanation of the same effectiveness of both drugs is that they are representatives of a well-known class of 4-aminoquinolines (3). However, this speculation probably is invalidated by the striking decrease of antimalarial activity from Q 25 to Q 1 when the hydroxyl of Camoquin (I*a*) is replaced by a hydrogen atom (I*c*). The inactivity of II*b* may perhaps be explained by the likelihood that a compound of that structure is more resistant to *in vivo* demethylation than O-methyl Camoquin. It has been suggested by Blanchard that the unexpected activity of a certain antimalarial, SN-15,085, may be based upon its demethylation *in vivo* to a hydroxy derivative (4). Further, demethylation of the well-known antimalarial quinacrine (atabrine) actually has been observed in man (5).

These considerations lead to the suggestion that O-methyl Camoquin may be demethylated by the chick to Camoquin, thus accounting for the identical effectiveness of the two drugs.

## REFERENCES

(1) Burckhalter, J. H., Tendick, F. H., Jones, E. M., Jones, P. A., Holcomb, W. F., and Rawlins, A. L., *J. Am. Chem. Soc.*, **70**, 1363(1948).
(2) Burckhalter, J. H., Tendick, F. H., Jones, E. M., Holcomb, W. F., and Rawlins, A. L., *ibid.*, **68**, 1894(1946).
(3) Wiselogle, F. Y., "A Survey of Antimalarial Drugs," 1941–1945, J. W. Edwards, Ann Arbor, Mich., 1946.
(4) Blanchard, K. C., *ibid.*, p. 134.
(5) Hammick, D. L., and Firth, D., *Nature*, **154**, 461 (1944); Hammick, D. L., and Mason, S. F., *ibid.*, **156**, 718 (1945).

* Received September 21, 1948, from the Department of Pharmaceutical Chemistry, University of Kansas School of Pharmacy, Lawrence.
† Camoquin is the Parke-Davis name for 4-(7-chloro-4-quinolylamino)-α-diethylamino-o-cresol. It was synthesized in the laboratories of that company (1), and has received promising clinical trials in many parts of the world.
‡ Both products have been assigned an activity of Q 25 against *Plasmodium gallinaceum* by Dr. R. J. Porter, University of Michigan, Ann Arbor (1, 3).

# The Absorption of Mercury Through the Skin*

By A. BASS and E. D. ROBINSON

**The penetration of mercury through the skin of rabbits has been assayed in the case of two mercury ointments which differ only in that one contains resorcinol. The assay consisted in measuring the mercury concentration of the kidneys after twenty-four hours of topical application. The kidneys of rabbits exposed to the resorcinol-containing ointment had an average mercury concentration only one-sixth that of the group exposed to the resorcinol-free ointment. In an assay for bacteriostatic power, using the Food and Drug Administration agar cup-plate method, the resorcinol-containing ointment gave an inhibition zone over twice as wide as that shown by the resorcinol-free ointment.**

IT HAS been reported recently by Laug, *et al.* (1), that, after suitable exposure to mercurial ointments, the penetration of mercury through the skin can be determined by analysis of the kidneys in terms of mercury concentration per gram of wet tissue.

This report deals with a similar study of the absorption of mercury from two commercial ointments which differ from each other in that one of the products contains resorcinol.

## EXPERIMENTAL

The formulas of the two ointments are given in Table I.

TABLE I.—OINTMENT FORMULAS

| | A, % | B, % |
|---|---|---|
| Petrolatum | 50.88 | 54.88 |
| Boric Acid | 2.12 | 2.12 |
| Anhydrous Lanolin | 20.00 | 20.00 |
| Beeswax | 10.00 | 10.00 |
| Resorcinol | 4.00 | 0.00 |
| Red Mercuric Oxide | 5.00 | 5.00 |
| Water | 8.00 | 8.00 |

Ointment A contains 5% red oxide of mercury and 4% resorcinol. Ointment B also contains 5% red oxide of mercury, but no resorcinol; the petrolatum in the second formula has been increased by 4% to replace the missing ingredient. All chemicals are U. S. P. XIII grade except the mercuric oxide, which is N. F. VIII.

The test animals were rabbits in place of the rats used by the above authors (1). Male albino rabbits, weighing 1.4 to 2.3 Kg., were clipped closely over the back. Ten grams of ointment were inuncted over an area of 30 square inches of clipped skin, the inunction being made for two minutes with a glass rod. Without removing excess ointment, the treated area was covered with a sheet of rubber cut from an inner tube, after which the rabbits were returned to individual cages. The rubber was held firmly in place by strips of adhesive tape which passed around the animal's abdomen, and was designed to prevent oral contact with the ointment. After twenty-four hours the animals were killed, both kidneys removed, weighed, and analyzed for mercury by a dithizone method (2). The color readings were made on a Klett-Summerson photoelectric colorimeter using a No. 50 filter. Eight rabbits were used for an assay.

In some cases the death of the animals was caused by asphyxiation with ether, in other cases the anesthetized animals were exsanguinated from the cut carotid artery. The analytical results gave no significant difference between these two methods of killing the rabbits.

The assay of the two ointments is shown in Table II. A series of controls on seven untreated rabbits failed to indicate any detectable mercury in the kidneys.

TABLE II.—ASSAY OF MERCURY OINTMENTS

| Weight of Both Kidneys in Gm. | Mercury Content, γ/Gm. Wet Tissue |
|---|---|
| Ointment A | |
| 12.9 | 4.4 |
| 14.2 | 3.5 |
| 12.4 | 4.1 |
| 14.4 | 4.2 |
| 15.3 | 5.5 |
| 14.7 | 4.4 |
| 11.0 | 4.3 |
| 12.0 | 6.9 |
| | Av. 4.7 |
| Ointment B | |
| 17.4 | 32 |
| 13.5 | 20 |
| 12.3 | 27 |
| 10.6 | 40 |
| 13.5 | 13 |
| 13.8 | 17 |
| 10.4 | 27 |
| 9.5 | 52 |
| | Av. 29 |

There is a striking difference between the action of the two ointments, by this twenty-four hour test. On the average, Ointment A permits a mercury concentration in the kidney of only one-sixth that found with Ointment B. The resorcinol, apparently, interferes with either the penetration of the mercury compound through the skin or its storage in the kidney after penetration.

The bacteria-inhibiting power of the two ointments was determined by the official F. D. A. agar

* Received May 5, 1949, from the Medical Research Division, Pluogh, Inc., Memphis, Tenn.

cup-plate method. The results are given in Table III and are the average of four samples in each case. For these determinations we are indebted to Dr. I. Michelson of the University of Tennessee Medical School.

TABLE III.—BACTERIOSTATIC POWER OF TWO MERCURY OINTMENTS

| | Zone of Inhibition, Mm. |
|---|---|
| Ointment A | 9 |
| Ointment B | 4 |

The heightened bacteriostatic power of Ointment A is probably due to the fact that resorcinol, itself an antiseptic, is quite soluble in water. Since the agar test medium contains much water the resorcinol in the ointment, particularly at the edge of the cup where the ointment is in contact with the agar, will dissolve and diffuse into the medium, thereby increasing the inhibition zone. It is open to question whether this same increase in bacteriostasis would be obtained under actual conditions of topical application. The testing under such conditions offers a difficult problem.

## SUMMARY

1. The penetration of mercury through the skin of rabbits has been assayed in the case of two mercury ointments, one of which also contains resorcinol.

2. The bacteriostatic power of the two ointments has been determined by the F. D. A. agar cup-plate method.

## REFERENCES

(1) Laug, E. P., Vos, E. A., and Kunze, F. M., THIS JOURNAL, **36**, 14(1947).
(2) Laug, E. P., and Nelson, K. W., *J. Assoc. Offic. Agr. Chemists*, **25**, 399 (1942).

# Note

## A Note on a Preliminary Observation of the Incompatibility of Vitamin $B_{12}$ and Ascorbic Acid*

By WALTER C. GAKENHEIMER and BEATE A. FELLER

IN THE course of investigating the pharmaceutical properties of vitamin $B_{12}$, a very pronounced incompatibility, observable within twenty-four hours, between this vitamin and ascorbic acid was discovered.

Solutions of crystalline vitamin $B_{12}$ (15 μg./cc.) and solutions of vitamin $B_{12}$ concentrate (equivalent to 15 μg./cc. of vitamin $B_{12}$) containing, in one series, 10 mg./cc. of ascorbic acid and, in a second series, 50 mg./cc. of ascorbic acid were prepared for stability testing. These four groups of solutions contained in each case 0.5% phenol. They were sterilized by filtration and subdivided aseptically into flame-sealed ampuls.

Assay results of the solutions containing ascorbic acid and vitamin $B_{12}$ (crystalline or concentrate) indicated more than 50% decomposition of the vitamin $B_{12}$ after storage at 28° to 30° for twenty-four hours, as determined by the cup-plate assay procedure (1), utilizing *Lactobacillus lactis Dorner* (2) as the test organism. The assays of control solutions containing no ascorbic acid indicated no vitamin $B_{12}$ decomposition.

There was no significant difference in the rates of vitamin $B_{12}$ decomposition in the presence of the two different ascorbic acid concentrations, but this is not surprising in view of the large excess of ascorbic acid in each case. In addition, it has been observed that the presence of 0.5% phenol does not significantly alter the rate of vitamin $B_{12}$ decomposition resulting from its incompatibility with ascorbic acid.

* Received October 22, 1949, from the Research Laboratories, Merck and Co., Inc., Rahway, N. J.

### REFERENCES

(1) Woodruff, H. B., and Foster, J. C., *Science*, in press.
(2) Shorb, M. S., *Science*, **107**, 397 (1948).

# Book Reviews

*Trace Elements in Food.* By G. W. MONIER-WILLIAMS. John Wiley and Sons, New York, 1949. viii + 511 pp. 13.5 x 21.5 cm. Price $6.

The trace elements in food are defined by the author of this book as those elements in food which are present to the extent of 0.005 per cent or less. This includes iron which, while not a trace element in the body, is a trace element in food.

Trace elements in food are important because they may be toxic or injurious; they may aid in the catalytic destruction of other vital substances, i.e., copper and vitamin C; or they may aid in causing off-color and off-flavor in food.

A few of the toxic trace elements, like selenium, may actually occur in the natural foodstuffs occasionally. Other elements like arsenic, lead, tin, and mercury are more apt to get in by way of industrial processing or spraying for insects and rodent control. The toxicology, biochemistry, and analytic chemistry of these elements are extremely important to the food technologist. It is fortunate that the author has seen fit to bring all these data together in one book.

Since the pharmacist must deal frequently with natural substances, he will often find a lead here in the control of his products, when trace elements may affect stability, color, or flavor.

In this book, each chapter discusses one element. If the element is essential for life, this fact is brought out with as much detail as is practicable or available. In such cases biological availability, minimum requirements, absorption, retention, excretion, and similar properties are brought out. The toxicity and its mode arriving in the foodstuffs are next taken up. The ability of foods to corrode metals is discussed if such action is of significance. The effect of the element on taste and color of individual foods is discussed when pertinent. Analytical methods (which are, by their nature, micro) close the chapters. References appear at the end of each chapter.

To those interested in any phase of food tecnology, this is an important and useful book.

*Radioactive Measurements with Nuclear Emulsions.* By HERMAN YAGODA. John Wiley and Sons, New York, 1949. lx + 356 pp. 13.5 x 21 cm. Price $5.

The detection of radioactive particles by means of exposure to photographic emulsions is a very useful technique in the radioactivity field. Dr. Yagoda has reviewed and brought together the methods of applying such techniques. Specialists in radioactivity will find this book a very useful guide to such methodology.

The bibliography contains about 700 items making up a nearly complete list of publications in this field.

Since this is an era of elaborate electronic recording apparatus, many will be pleased to note the value of such a "primitive" device as a photographic plate.

*New Gould Medical Dictionary.* First Edition Edited by DRS. HAROLD WELLINGTON JONES, NORMAN L. HOERR, and ARTHUR OSOL. The Blakiston Co., Philadelphia, 1949. xxviii + 1294 pp. 17 x 25 cm. 252 illus. Price $8.50.

The *New Gould Medical Dictionary* is the excellent answer to a long-felt need. It is the first completely new unabridged medical dictionary issued in the last thirty-eight years, and the first medical dictionary to be built on modern lexicographic methods.

Planned from the beginning as a new entity, this book is the product of an editorial board and distinguished staff of more than one hundred contributors. Thousands of new entries from all branches of medicine and allied sciences are presented. New terms, as well as changes in usage, are given and pronunciation is indicated by a simple system of phonetic respelling. Much of the illustrative material is entirely new and in full color, and the tables of hormones, vitamins, enzymes, etc., are in a section of their own for the first time.

Legibility is of a high degree of excellence, due to careful choice of type styles, and subentries are aligned for the first time. All entries are presented in a single inclusive alphabetical list. This book should mark a new era in medical dictionary making.

Dr. Arthur Osol, one of the editorial trio, represents the pharmaceutical and chemical field, and because of the meticulous attention given to entries in this area by him, members of the pharmaceutical profession will find the dictionary particularly valuable.

The book is sturdily constructed and will stand up under long continuous use. The paper, binding, and printing are of the usual high degree of excellence found in books published by the Blakiston Company.

*Industrial Toxicology.* By LAURENCE T. FAIRHALL. Williams and Wilkins Co., Baltimore, 1949. xi + 483 pp. 15 x 23 cm. Price $6.

*Industrial Toxicology* is a reference manual describing the toxicity of both old and new substances used in industry. The author describes, under each listing, the characteristics, industrial uses, toxicity and analysis and includes a carefully selected list of pertinent references.

Many of the substances covered are of interest pharmaceutically—iodine mercury, acetone, benzene hexachloride, carbon tetrachloride, chloroform, dibutyl phthalate, 2,4-D-ethylacetate, ethyl alcohol, ethyl chloride, formaldehyde, methanol, nitroglycerin, oxalic acid, phenol, picric acid, isopropyl alcohol, methanolamine, and turpentine to mention a few.

The conciseness of its organization makes this reference a valuable book to industrial hygienists and to all who have occasion to refer to this kind of information.

*Organic Chemistry.* 3rd ed. By ELDIN V. LYNN. Lea and Febiger, Philadelphia, 1948. 355 pp. 15 x 25 cm. Price $4.50.

The third edition of Dr. Lynn's *Organic Chemistry* represents a modernized version of the previous editions of the book. Those familiar with the earlier editions will find that the original material has been revised to include many of the more recently introduced medicinal compounds.

None of the forty-four chapters is exceptionally long but a great deal more material is included in the text than an initial cursory glance would indicate. While there are some good reasons for such a large number of chapters, certainly some of them could be grouped together. The chapters otherwise follow the scheme generally used by authors of organic texts. Following each chapter are questions which are rather stereotyped.

The book is well-bound and printed on heavy paper which will undoubtedly take much use. The printing itself is rather small and closely spaced. Students may find reading for prolonged periods of time rather eye-straining. The chapters covering the beginning phases of organic chemistry (aliphatics and benzene derivatives) are inclusive enough and probably satisfactory for a beginning course in organic chemistry. The chapters on specialized material such as heterocycles, alkaloids, dyes, proteins, enzymes and volatile oils are too terse and contain many structures and names without adequate explanation or meaning. Students will not find these latter chapters very stimulating.

Teachers in schools of pharmacy who use the book as a beginner's text in organic chemistry will find it adequate for the most part. The many medicinal compounds included, though often dismissed in one sentence, will probably add student interest. The book would not be satisfactory for a course in the chemistry of medicinal products, but the author does not intend it for that purpose. For most teachers in schools of chemistry the book would be considered inadequate for an A. C. S. course in organic chemistry. Purchasers interested in a reference for medicinal compounds would find an advanced text more desirable.—WARREN E. WEAVER.

*Précis de Microscopie, Collection des Précis Medicaux.* MASSON, EDIT. 7th ed. Paris, 1949. 1430 pp. + 392 figures. 2600 francs.

The seventh edition of this well-known Handbook of Microscopy is quite up-to-date, and discusses problems of interest in the field of scientific and practical pharmacy, taking into account data available from the literature up to, and including, 1948.

Part I discusses not only the use of the conventional optical microscope in the study of stained material, but also the use of the phase microscope and electron microscope.

Part II discusses physicochemical problems related to H ion concentration (*p*H), redox-potentials (rH), osmotic pressure, solubility, polarization, melting and boiling points, properties of synthetic resins and varnishes, and includes a wealth of information about physical and chemical constants.

Part III presents a critical discussion of the "special methods" for study of amoeba, flagellas, spirochetes, vires, bacteria, and, in general, methods of pharmacognosy and legal medicine.—J. DUFRENOY.

*The British Pharmaceutical Codex 1949.* Published by Direction of the Council of the Pharmaceutical Society of Great Britain. The Pharmaceutical Press, London, 1949. xxv + 1562 pp. 14 x 23 cm. Price £3. 3.0.

The significance of the British Pharmaceutical Codex in Great Britain is somewhat comparable to that of the National Formulary in the United States, although the scope of the former is much more inclusive. The British Pharmaceutical Codex is published by direction of the Council of the Pharmaceutical Society of Great Britain. It is revised by a committee, the members of which are elected by that Council. The standards of the Codex have been recognized as official by the British Food and Drug Act since 1938.

The 1949 edition of the Codex is the fifth to have been published since it first appeared in 1907. It continues to be a book of reference for pharmacists and medical practitioners, but in this edition greater emphasis than heretofore is placed on adequate standards of strength, quality, purity, and identity for drugs not included in the British Pharmacopœia. The new edition is divided into six parts, the first of which includes general monographs on drugs. The second part contains much useful information on antitoxins, vaccines, and related substances, while the third, fourth, and fifth sections are devoted, respectively, to preparations of human blood, ligatures and sutures, and surgical dressings. The sixth part of the 1949 Codex, comprising about one-fourth of the entire book, is a formulary of preparations not official in the British Pharmacopœia but which are used in England. Brief descriptions of drugs included in the previous edition of the Codex are given in an appendix.

In the revision leading to the publication of the 1949 edition of the Codex many monographs were deleted because the drugs did not meet clinical, pharmacological, or pharmaceutical requirements. At the same time many new monographs were added, particularly on newer chemotherapeutic agents. The trend away from the use of botanical drugs and toward the wider recognition of synthetic organic medicinals is quite noticeable in the 1949 Codex. The British Pharmaceutical Codex has always been more than a book of standards for drugs. In the monographs on basic drugs, for example, a short description of a method of manufacture is invariably given. In addition to this the action and uses of all drugs are stated briefly, but in sufficient detail to impart to the pharmacist information of this nature which he might be expected to have readily available. Drugs listed in the British Pharmacopœia are also included in the Codex. The standards for these drugs, however, are not reproduced in detail, but references are made to the original source. Information on action and uses of the British Pharmacopœia drugs is, however, invariably presented. While the British Pharmaceutical Codex is planned to serve the needs of British pharmacists, many in the United States will find it an unusually useful reference book relating to many drugs which are widely used in this country. The printing and binding are of good quality and the Codex Revision Committee deserves commendation for the excellence of their accomplishment in bringing out a new edition of this useful book.

*Streptomycin—Its Nature and Practical Application.* EDITED BY SELMAN A. WAKSMAN. Williams & Wilkins Co., Baltimore, 1949. ix + 618 pp. Illustrated. 15 x 23.5 cm. Price $10.

The organism-producing streptomycin was first isolated by Dr. Selman A. Waksman of the Department of Microbiology of the New Jersey Agricultural Experiment Station, Rutgers University, in 1943. Announcement of the isolation of streptomycin was made early the following year. The phenomenal rise of streptomycin since the announcement of its isolation is familiar to all members of the pharmaceutical profession. Nearly 1800 publications relating to the development and utilization of streptomycin have appeared since 1943. In this book an attempt has been made to summarize the present status of the subject. Even a cursory examination of the text indicates that this attempt has been quite successful. The book is divided into four sections. The first section covers the microbiological and chemical aspects of streptomycin and includes a historical introduction and a chapter on *Streptomyces griseus* by Dr. Selman A. Waksman, the editor. The second section relates to antibacterial and pharmacologic properties of streptomycin and includes nine chapters. In the third, section, the most extensive of the four, the clinical uses of streptomycin are discussed while in the fourth section miscellaneous uses of the drug are covered. The several chapters of the book have been written by contributors, all of whom are outstanding authorities in their fields and many of whom pioneered in the development and application of streptomycin. No attempt has been made to include a complete bibliography on streptomycin since this was covered in a publication entitled "The Literature of Streptomycin 1944–1948" published by the Rutgers University Press. Each chapter in the book, however, is followed by a selected list of particularly pertinent references. The authoritative nature of this book makes it an ideal source of information for anyone interested in any subject relating to streptomycin.

*Hipodermoterapia—Tecnica Farmaceutica de las Preparaciones Inyectables.* 1st Spanish edition. BY HUGO CAZZANI. Editorial ALFA, Buenos Aires, 1949. Illustrated. xix + 950 pp. 16 x 23 cm. Price $18.

This book is a Spanish translation of an Italian treatise on the pharmaceutical technique of injectable preparations. It consists of three sections, the first of which describes methods and equipment for the sterilization, preparation, filling, preservation and control of parenteral solutions. Attention is also directed to standards for glass containers and the influence of different types of glass on solutions intended for injection. In the second part of the book, entitled "Dictionary of Injectable Preparations," methods of preparation are given for nearly every conceivable type of parenteral solution. The book also includes a bibliography and an author and subject index. The book includes very little information with which a manufacturer of parenteral solutions is not familiar. Despite this, it might serve a useful purpose as a reference book for hospital pharmacists and others concerned with the preparation of parenteral solutions.

*Principles and Practice in Organic Chemistry.* BY HOWARD J. LUCAS AND DAVID PRESSMAN. John Wiley and Sons, New York, 1949. xi + 557 pp. 15 x 23.5 cm. Price $6.

This is a very carefully prepared laboratory text for first-year organic chemistry. The student is first made familiar with the simpler apparatus by such experiments as calibration of thermometers, determination of distribution coefficients and melting points, and then he is gradually led into more complex experiments involving special techniques and apparatus. Experience with simple fractionating columns, vacuum distillation apparatus, chromatograph columns, and phase separators is included, along with several other techniques not too commonly found in elementary lab manuals; yet the equipment is either of very simple design or is set up by combining common apparatus, thus being quite practical for the teaching laboratory.

Along with each type of synthesis or experiment is included a discussion of the theory and principles involved. Of particular interest to the instructor and value to the student are the discussions of possible side reactions and means of reducing amounts of by-products.

There are very clear and thorough directions for note-keeping in the beginning of the book and a set of questions, largely dealing directly with the experiment at hand, along with each type of reaction.

This book should be examined by every teacher of organic chemistry, for it presents a very well organized laboratory course that should prove greatly stimulating both to teacher and student.

*The Givaudan Index—Specifications of Synthetics and Isolates for Perfumery.* Givaudan-Delawanna, Inc., New York, 1949. 378 pp. 15 x 23.5. Price $5.

In this book are assembled specifications for synthetic organic chemicals and essential oil isolates used in the fabrication of perfumes. Many of these products, in addition to being used in the perfume industry, are also employed as flavors and perfumes in pharmaceutical preparations. Although the book was compiled by the members of the staff of Givaudan-Delawanna, Inc., to serve as a manufacturer's publication it should also create considerable pharmaceutical interest. The chemicals described are arranged alphabetically from acetanisole to zingerone. The information in each monograph includes, in addition to the usual English name, the French, German, and Spanish equivalents. These are followed in order by the structural formulas and the chemical names used by *Chemical Abstracts*. Other data relating to each chemical include physical and chemical criteria of quality and purity. Of particular interest is information concerning the use which includes suggestions as to the types of compositions in which each chemical may be employed to the best advantage. Analytical procedures applying to the chemicals described are outlined quite in detail in an appendix. The value of the book is enhanced by an odor classification of aromatic chemicals, a foreign language index of French, German, and Spanish names, and an index of specifications. The typography of *The Givaudan Index* has been well chosen for attractiveness and easy reading.

*Pharmakologische Methoden zur Auffindung von Arzneimitteln und Giften und Analyse ihrer Wirkungsweise.* By LEOPOLD THER. Wissenschaftliche Verlagsgesellschaft m. b. H. Stuttgart, 1949. 460 pp. 16.5 x 23.5 cm. Price DM 32.

The book is written for the purpose of giving detailed descriptions of various pharmacological methods which are useful in a study of drugs and poisons. Special emphasis is placed on those methods which permit evaluation and classification of drug action in the living cell both in the intact animal and in isolated organs. Not included are procedures for the study of vitamins, hormones, and metabolism as well as chemotherapeutic investigations using microorganisms or enzyme systems.

The material is divided into 18 chapters, four of which treat general subjects. The chapter on mathematical methods is very useful. It is written in simple and clear language, and it covers practically all problems which are needed in an evaluation of the usual pharmacological investigations.

The main chapters on the various pharmacological methods are arranged according to the anatomical systems or organs which are affected by the substance under investigation. The description is in most instances easily understandable, and it is supported by numerous drawings and many tabulated examples.

As to the material presented, two shortcomings of the book are quite obvious. The first and minor one concerns the fact that the author very often lists several procedures without any critical evaluation of their advantages and disadvantages for a given problem. The second and more important objection lies in the incompleteness of the methods described in this book. A survey of the numerous references at the end of each chapter shows clearly that the material was taken almost exclusively from the German literature. This applies not only to the war years but also to the preceding period. As a consequence, the book lacks many methods reported in the American or English literature before 1939, while the more recent developments are missing entirely. This is true not only for advances in equipment and techniques as applied to older methods described in the book, but it concerns also completely new fields of pharmacological investigations such as, for instance, the study of anticonvulsive drugs.

However, if one recognizes these limitations the book may be very helpful for the large amount of descriptive information which is often difficult to find outside of well stocked libraries—GEORG CRONHEIM.

*Pharmaceutical Laboratory Manual.* By R. A. KUEVER. J. B. Lippincott Co., Philadelphia, 1947. x + 290 pp. 16 x 24 cm. Price $2.75.

This book is a typical laboratory manual in Galenical pharmacy. Directions are given for conducting experiments and the students are asked a number of questions involving reference work, calculations, reasoning by analogy, and other problems.

It is difficult for the reviewer to see the need for outlining preparations of six different aromatic waters and four pills as well as several obsolete preparations.

A simplified glossary of common words used in pharmacy will no doubt be useful to the novice.

*Textbook of Organic Chemistry.* 3rd ed. By HUGH C. MULDOON. The Blakiston Company, Philadelphia, 1948. viii + 648 pp. 15 x 25 cm. Price $5.50.

The third edition of Dean Muldoon's *Organic Chemistry* represents a thoroughly revised and modern text on organic chemistry with a pharmaceutical flavor. Whether the book achieves the author's purpose of providing beginners with a good fundamental background in organic chemistry supplemented by medicinal chemistry, is doubtful.

*Organic Chemistry* follows the conventional order of most organic texts in covering aliphatic hydrocarbons, halides, alcohols, ethers, carbonyls, acids, nitrogen compounds, and carbohydrates, in that order; followed by aromatics in the conventional sequence. The last few chapters are devoted to heterocycles, terpenes, alkaloids (and glycosides), dyes, enzymes (and antibiotics), and finally a very compact chapter on steroids, hormones, natural pigments, and vitamins. The appendix includes a glossary and bibliography.

Each chapter includes the chemically related compounds of the U. S. P., N. F., and N. N. R. The author's style is direct and easily understood and, in general, the explanations are above reproach. The text is attractively and sturdily bound, the cover being an unusual display of structural formulas of medicinals and other organic substances. In general, the accuracy of material, as given, is very satisfactory although the text and the cover unfortunately bear a structure for $\beta$-carotene minus a double bond in the ring.

This book will be valuable to those who teach a course in organic chemistry using medicinal products illustrative of the techniques of that science. It will not meet the demands of a truly satisfactory course in organic chemistry nor of a course in medicinal products taught following a basic organic course. There is too great a tendency to oversimplify the subject and yet at the same time present the structures of complex medicinals which demand a most stringent course of training in organic chemistry. However, Dean Muldoon has made a gallant effort to reconcile that which ordinarily would seem irreconcilable. Active practitioners of the medical sciences would doubtless be in a somewhat better position through the purchase of a book written more exclusively for the chemistry of medicinal substances.—WARREN E. WEAVER.

*Schimmel 1946 Annual Report on Essential Oils, Aromatic Chemicals, and Related Materials.* Schimmel and Company, Inc., New York, 1949. 137 pp. Illustrated. 15 x 23 cm. Price $3.

The newly published 1946 Schimmel Report has recently become available and appears to be a volume of more than usual interest. The 1946 report covers developments in the field of aromatics during that year. Among the subjects covered are methods of analysis, analytical characteristics and standards, the pharmacology of essential oils, biogenesis of perfume materials and miscellaneous industrial products. Statistical data on production, exports, and imports of the main essential oil producing and importing countries of the world are summarized. A bibliography of more than 150 references to publications relating to essential oils and aromatics which appeared in 1946 is included.

*The Essential Oils. Volume II (The Constituents of Essential Oils).* By ERNEST GUENTHER. D. Van Nostrand Company, Inc., New York, 1949. xiii + 852 pp. 15 x 23 cm. Price $10.

In the second volume of *The Essential Oils* the standard of excellence established in the first volume [THIS JOURNAL, **37** 214(1948)] published in 1948, which covered the history, origin in plants, production and analyses of essential oils, has been maintained. In the second volume the constituents of essential oils including the hydrocarbons, the terpenes, the sesquiterpenes and their oxygenated derivatives are discussed quite completely from the standpoint of occurrence, isolation, identification, properties, and use. A particularly interesting and useful feature of the second volume of *The Essential Oils* is a section by Frances S. Sterrett, Research Chemist of Fritzsche Brothers, Inc., on the preparation of derivatives of essential oil constituents. This chapter will serve adequately as a guide for the preparation of crystalline derivatives useful in the identification of essential oil constituents. Like the first volume, the second is well documented throughout and the printing and binding are of excellent quality. All who are interested in essential oils from an academic standpoint will find Volume II of especial interest, and those concerned with essential oils from either a practical or research viewpoint will find the book an extremely useful tool. The authors are to be congratulated upon the excellence of their presentation.

*Ion Exchange—Theory and Application.* EDITED BY FREDERICK C. NACHOD. Academic Press, Inc., New York, 1949. xii + 411 pp. Illustrated. 15 x 24 cm. Price $8.50.

This timely publication by sixteen co-authors gives a thorough scientific and practical discussion of the properties and uses of ion exchange resins. A brief historical introduction is given, followed by chapters treating the equilibria and kinetics of the systems involved in ion exchange. The authors included most of the approaches to mathematical expression of exchange reactions, pointing out the advantages and disadvantages of each, rather than selecting any single method. This type of treatment makes the book of much greater value. The structures and types of resins are presented along with results obtained in various applications of different types. A description of commercial ion exchange apparatus and its operation is included, and detailed review of the use of resins in deionizing water is given. The applications of ion exchange to the separation or isolation of inorganic ions, metabolic products, alkaloids, amino acids, and miscellaneous organic compounds are reviewed, these chapters being especially interesting to the field of pharmacy. The methods that have been used for evaluating resins are also presented.

This book fills a great need of scientific workers for a thorough review of ion exchange and its applications, and it furnishes the background information necessary to planning conclusive experiments for the evaluation of resins for a given task. Newcomers to the field of ion exchange will find this book particularly valuable. It should stimulate a much wider interest in further applications of ion exchange resins.

*Stedman's Medical Dictionary.* 17th revised edition. EDITED BY NORMAN BURKE TAYLOR. Williams & Wilkins, Baltimore, 1949. xliv + 1361 pp. Illustrated. 15 x 24 cm. Price $8.50 with thumb index; $8.00 without thumb index.

For many years *Stedman's Medical Dictionary* has been a useful tool for anyone using medical and pharmaceutical terms. This seventeenth edition has been revised with particular attention directed toward the deletion of obsolete words, the revision of certain definitions, and the addition of new material. The derivation of scientific words used in medicine and related sciences included in this dictionary is a particularly useful feature. For the first time biographical sketches of outstanding individuals in the history of medicine have been included. The section on etymology, descriptions of techniques of clinical laboratory tests, and tables appearing in previous editions have been continued. The book purports to include information on pharmaceutical preparations official in the United States Pharmacopœia and the National Formulary, but on the page bearing the copyright notice acknowledgment is made of the use of certain portions of the text of the eleventh revision of the United States Pharmacopœia and the sixth edition of the National Formulary. This might lead one to believe that certain portions have not been as thoroughly revised and brought up to date as they possibly should have been. A spot check of this particular feature of the dictionary unfortunately confirms that belief.

*Outline of Biochemistry.* 3rd ed. Edited by Ross AIKEN GORTNER, JR. John Wiley and Sons, New York, 1949. xvi + 1078 pp. 14.5 x 23 cm. Price $7.50.

It has been eleven years since this excellent and authoritative textbook, originally written by one of the American biochemical pioneers, was revised. During that period biochemistry, like any active science, has progressed materially. It is fitting, therefore, that the book should be, and is, thoroughly revised and enlarged.

Dr. Gortner's book will appeal to many concerned with pharmacy because of its approach which is physical and chemical as opposed to the biological and the medical approach. It contains, probably because of the author's interest in agricultural chemistry, considerable plant biochemistry, most of which is missing from other standard texts. The section on applied physical chemistry (chiefly colloidal chemistry) is one of the best treatises of its kind the reviewer has seen.

The sections on intermediate metabolism have been completely revised and modernized and many changes have been made in the chapters on hormones and vitamins. The section on plant pigments is written in an interesting manner, from the biochemical-genetic point of view.

The chapter on protein denaturation is new to this edition, as are chapters on fat metabolism and carbohydrate metabolism.

In all cases the present collaborators have succeeded in preserving the spirit of the former editions. The book is well bound in an attractive cover and the typography is up to the usual high standards of the publisher.

*The Official Preparations of Pharmacy.* By CHARLES OREN LEE. C. V. Mosby Company, St. Louis, 1949. 528 pp. Illustrated. 13.5 x 22 cm. Price $5.50

The purpose of this book is to discuss the problems relating to the manufacture of the pharmaceutical preparations official in the United States Pharmacopœia and the National Formulary. It is intended to serve as a textbook for a one-term course in pharmaceutical technology. The book is divided into 25 chapters, each of which is devoted to a single type, or closely related types, of pharmaceutical preparations. The general discussions in each chapter include definitions and descriptions of processes involved in the manufacture of the preparations under consideration. This is followed by the presentation of pertinent information relating to the individual preparations which are listed alphabetically. The book should serve adequately as a reference and textbook in an introductory course on official pharmaceutical preparations.

*Quantitative Pharmaceutical Chemistry.* 2nd ed. By GLENN L. JENKINS, ANDREW G. DU MEZ, JOHN E. CHRISTIAN, AND GEORGE P. HAGER. McGraw-Hill Book Co., New York, 1949. xii + 531 pp. 13.5 x 20.5 cm. Price $4.75.

This well-known text and laboratory guide in quantitative pharmaceutical chemistry has been revised to bring it in line with changes in the United States Pharmacopœia and the National Formulary. In addition, two new junior authors have been added to the undertaking.

In general, the second edition follows the pattern of the first. The book is divided into 3 components: general methods used in official analyses, physical methods used in official analyses, and special methods used in official analyses. No attempt is made to include all official analyses, but typical ones are selected and given in detail, and by the use of tables the reader is referred to similar procedures. The explanations of the chemistry involved in the assays are exceedingly useful, and in many cases these explanations occur in no other publication.

Unfortunately, the authors did not change the method for determining the melting range. This method was given incorrectly in U. S. P. XII and calls for the "stem correction" even though provision is made for the use of partial immersion thermometers. In U. S. P. XIII this was corrected. Since the error in U. S. P. XII caused so much confusion, it is regrettable that the authors neglected to make this change.

In the first edition there were explanations given for certain assays involving unusual factors. These explanations were not carried over into the second edition. The assay for bromides in Three Bromides Elixir may be cited as a case in point. In this assay each cc. of 0.1 *N* silver nitrate is equivalent to 0.01059 Gm. of total bromides. The derivation of this factor is not easy for an uninitiated person to visualize. The inclusion of the derivation in the first edition was, therefore, a definite contribution which should not have been omitted.

The reviewer has had occasion to refer to this book many times in the past, and has found it useful. No doubt it will be especially useful as a textbook to those who teach courses in drug analyses. Certainly the revision will be welcomed by many users.

*Patent Law.* By CHESTER H. BIESTERFELD. 2nd ed. John Wiley and Sons, New York, 1949. viii + 267 pp. 15 x 23 cm. Price $5.

Sooner or later most pharmaceutical scientists must come up against the patent situation. Of course scientists cannot be expected to be patent attorneys, but they can be expected to know enough of the elementary principles of patent law and functions to be able to cooperate intelligently with the patent attorney.

*Patent Law* is the best source of patent information from the scientists' viewpoint the reviewer has seen. The subject is presented in an orderly fashion and represents general and basic principles of substantive patent law without the multitude of fine legal distinctions which are so often hazards for the layman. In short, here is a book where the reader can "see the forest." The basic principles appear to be supported by carefully chosen actual cases, especially the citation of pertinent decisions of the Supreme Court and the Federal courts of appeal.

Typical chapter headings are: Invention and Discovery, Novelty, Priority of Invention, Originality, Abandonment, Permissible Breadth of Chemical Claims, Functional Claims, Double Patenting, Reissues, Infringement, Licenses, Patent Litigation, and Trade Secrets.

An appendix containing certain excerpts from the law, a bibliography, a table of cases, and a subject index complete the book.

*Organic Reactions. Volume V.* EDITED BY ROGER ADAMS. John Wiley and Sons, New York, 1949. viii + 446 pp. 15 x 23.5 cm. Price $6.

This is the fifth of the Organic Reactions series, which is increasing in importance and value to the organic chemist with the addition of each volume. This volume is written in the same style as the previous ones, is well referenced, and the selection of reactions presented is good. The Synthesis of Acetylenes, Cyanoethylation, The Diels-Alder Reaction: Quinones and Other Cyclenones, Preparation of Aromatic Fluorine Compounds from Diazonium Fluoborates: The Schiemann Reaction, The Friedel and Crafts Reaction with Aliphatic Dibasic Acid Anhydrides, The Gattermann-Koch Reaction, The Leuckart Reaction, Selenium Dioxide Oxidation, The Hoesch Synthesis, and The Darzens Glycidic Ester Condensation are included in this issue. It is hoped that the promptness of publication of these volumes will continue, for the set is rapidly becoming one of the outstanding references of organic chemistry.

*Chymia: Annual Studies in the History of Chemistry. Volume I.* TENNEY L. DAVIS, Editor-in-Chief. University of Pennsylvania Press, Philadelphia, 1948. xiv + 190 pp. 15 x 23.5 cm. Price $3.50.

*Chymia* is a new annual publication in the history of chemistry. The publication is an outgrowth of the Edgar Fahs Smith Collection in the History of Chemistry at the University of Pennsylvania. Professor Smith was always intensely interested in historical background in the sciences, especially chemistry. During his lifetime he had hoped to see a journal devoted to this field published. Although this never came to pass, *Chymia* is a fitting substitute.

Although Volume I of this new publication contains many scholarly articles of interest to chemists, perhaps pharmacists will be most interested in "The Early Chemical and Pharmaceutical History of Calomel" by our own Dr. George Urdang.

Although most of us cannot have the opportunity of browsing through the Smith Collection, *Chymia* brings much of the spirit of the collection into our homes in an informative and interesting fashion.

*America's Health, A Report to the Nation.* By The National Health Assembly. Official Report. Harper and Brothers, New York, 1949. xiv + 395 pp. 15 x 23 cm. Price $4.50.

In May, 1948, the National Health Assembly convened in Washington at the behest of the President of the United States in order to consider the entire question of public health policy for the next decade. This is the official report of that assembly.

The Assembly comprised about 800 representatives of professional organizations and public and private agencies. A group of 38 outstanding persons were selected as an executive committee. Pharmacy was represented on this committee, whose members were consulted both individually and as a group on all basic decisions, by Dr. Robert P. Fischelis, Secretary and General Manager of the AMERICAN PHARMACEUTICAL ASSOCIATION. Fourteen divisions, each representing a key health problem, made up the Assembly and each of these divisions is represented in this report as a chapter. The following subjects were covered:

What Is the Nation's Need for Health and Medical Personnel?
What Is the Nation's Need for Hospital Facilities, Health Centers, and Diagnostic Clinics?
What Is the Nation's Need for Local Health Units?
Chronic Disease and the Aging Process.
A National Program for Maternal and Child Health.
A National Program for Rural Health.
What Is the Nation's Need for Research in the Service of Health?
What Is the Nation's Need for Medical Care?
State and Community Planning for Health.
Physical Medicine and Rehabilitation.
What Can Be Done to Improve Dental Health?
A National Program for Mental Health.
What Can Be Done to Improve Nutrition?
A National Program of Environmental Sanitation.
International Cooperation in Health.

We hear much of medical-care programs these days, and much of the basis for any discussion originates with this report of the National Health Assembly. This is the "Pharmaceutical Survey" of the medical-care field, and pharmacists would do well to study it.

*Bentley's Textbook of Pharmaceutics.* 5th ed. REVISED BY HAROLD DAVIS. Williams & Wilkins, Baltimore, 1949. xiv + 1100 pp. Illustrated. 14 x 22 cm. Price $7.50.

This useful textbook, the first edition of which appeared in 1926, is well and favorably known to pharmaceutical educators and pharmacists of the United States because of the excellence of the organization and presentation of its subject matter.

Due to the death in 1943 of Arthur Owen Bentley, the author of the previous editions, the fifth edition has been revised by Harold Davis, Chief Pharmacist of the University College Hospital of London, with the collaboration of M. W. Partridge and A. I. Robinson. The major author and editor has retained as much as possible of the previous edition, but all parts have been carefully edited and the sections (V and VI) on pharmaceutical microbiology and on surgical dressings, sutures, and ligatures have been completely rewritten. Part I of the book includes a short history of the British Pharmacopœia and Part II explains the general principles involved in pharmaceutical operations. In Part III pharmaceutical manufacturing is stressed while Part IV is concerned mainly with the general principles involved in dispensing. In Part VII systematic consideration is given to the preparations of the 1948 British Pharmacopœia and selected galenicals of the British Pharmaceutical Codex. In this section reference is also made to many drugs of the United States Pharmacopœia which are identical with or resemble those in the British Pharmacopœia. Despite the fact that this textbook and reference book is written from the standpoint of the needs of British readers, many parts of it are of universal application and interest. Practicing pharmacists, teachers, and students of pharmacy will find this new fifth edition of *Bentley's Textbook of Pharmaceutics* an unusually interesting and useful reference book.

*Lange's Handbook of Chemistry.* 7th ed. EDITED BY NORBERT ADOLPH LANGE. Handbook Publishers, Sandusky, Ohio, 1949. xvi + 1920 pp. 13 x 20 cm. Price $7.

The editor of this useful handbook states in the preface to the new seventh edition that first consideration has been given to a thorough revision of materials previously presented instead of merely adding new tables without bringing standing material up to date. The use of this book as a reference during several weeks will lead the user to believe that this aim has been adequately accomplished. A fairly high proportion of tables which have appeared in previous editions have been extended or completely rewritten and a number of tables not in the previous editions are now offered for the first time. Among the tables included for the first time are: Abundance of the Elements; Glyceride Content of Drying Oils; Properties of Hormones; ASTM Classification of Coals by Rank; Formulas for Calculating Mineral-free BTU and Fixed Carbon; Density of Fuming Sulfuric Acid Solutions; Dielectric Constants; Dipole Moments; Mass of Water in Saturated Air; Partial Pressures of Aqueous Ammonia Solutions; Kopp's Rule for Calculating Specific Heat; Logarithms of Equilibrium Constants; Viscosity of Aqueous Sucrose Solutions; and Viscosity of Aqueous Ethyl Alcohol Solutions.

*Lange's Handbook of Chemistry* is so inclusive in its scope that it should be useful as a reference to anyone having to do with any phase of chemistry. Pharmaceutical chemists and pharmacists will find in the new edition, as in previous editions, much significant and frequently needed reference material of interest to them.

*Obstetric Analgesia and Anesthesia.* By FRANKLIN F. SNYDER. W. B. Saunders Co., Philadelphia, 1949. viii + 401 pp. 15 x 23 cm. Price $6.50.

Pharmacology and therapeutics textbooks and reference books which are modern and thorough include much data on the properties and uses of the most important drugs. However, the specialized use of drugs in a limited area is often only touched upon or even entirely omitted. High potency is the rule today rather than the exception when it comes to the consideration of modern drugs, and consequently it is important that books such as this one be written to provide information in these limited areas.

Since it is said that escape from the uterine environment is, from the mortality viewpoint, the most dangerous experience of life, analgesic drugs must play a much more important role in labor than the simple conquest of pain. Since fetal respiratory injury is the most frequent cause of mortality associated with birth and since most analgesics and anesthetics tend to alter the respiratory function, it is obvious that pharmacologic studies dealing with the effect of drugs on fetal respiration are of great importance.

The author divides this book into two parts, the first of which deals with respiratory injuries in the child. It covers the fundamentals of fetal respiration and the three respiratory pathologies most frequently encountered—asphyxia, atelectasis, and pneumonia. A laboratory method is described for assaying the effects of various anesthetic agents upon the mother and the fetus.

The second portion of the book deals with the treatment of pain during labor. Here individual drugs are considered in relation to labor and the three pathologies just mentioned.

Hospital pharmacists will have occasion to refer to this book frequently and other pharmacists will find it valuable for background.

*Advanced Organic Chemistry.* 2nd ed. By G. W. WHELAND. John Wiley and Sons, N. Y., 1949. xi + 799 pp. 15 x 23.5 cm. Price $8.

This book was designed to fill the need for a second-year textbook in organic chemistry, and it is intended to give the student a more thorough understanding of molecular structure, making possible, thereby, more accurate prediction of reactivity. It does not contain the special topics, such as sulfur compounds, metallo-organic compounds, the alkaloids, etc., that one usually finds in the advanced textbooks, but rather it is a book well designed to fill the gap between elementary organic chemistry and the special topics. It is of special value as an introduction to electronic interpretations of organic reactions.

The author has included brief but maturely written historical backgrounds for the modern concepts of organic chemistry. The reader is given a better understanding and perspective with regard to such developments as the Wöhler Synthesis, the theory of van't Hoff and Le Bel, and the concepts of acids and bases.

Although the book is woven about the structure of molecules, the illustrative examples include a majority of the reactions that are commonly included in second-year organic chemistry. Some classified reactions such as 1,2-shifts, allylic rearrangements, and the Claisen rearrangement are discussed separately and in good detail. As would be expected, the book contains excellent treatises on tautomerism, resonance, free radicals and stereoisomerism.

This book, as noted by the author, should be recommended only to the student who has completed physical chemistry, since the author has not hesitated to use the physicochemical principles in discussing structure and reactivity.

References are well selected, especially with regard to review articles of special subjects.

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## WHO MAKES IT?

The National Registry of Rare Chemicals, Armour Research Foundation, 33rd, Federal and Dearborn Streets, Chicago, Ill., seeks information on sources of supply for the following chemicals:

4-Nitroquinoline
4,8-Diaminoquinoline
4-Hydroxyquinoline
2-Methylimidazole
4-Methylimidazole
2,4-Dimethylimidazole
2-Hydroxymethylimidazole
4-Hydroxymethylimidazole
Tartronic acid
1,2,3,-Trichlorobenzene
7-Amino-*n*-caprylic acid
6-Aminoheptoic acid
Berbamine
Jervine
Pyridine-3,5-dicarboxylic acid
4,6-Diaminoquinaldine
Sphaerophorin
Atraric acid
Berberine
8-Hydroxyquinaldine

# JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

*Published in Two Monthly Editions under Supervision of the Committee on Publications with the Approval of the Council*

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## SCIENTIFIC EDITION

*Editor*

JUSTIN L. POWERS

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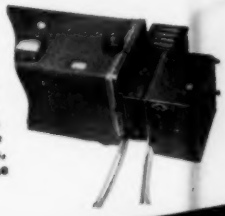
### Enables temperature control of sample compartment

A corrosive-resistant, light-tight, metal plate contains internal coils for circulating constant temperature fluid. Thermospacers mount directly on standard instrument. Can be used singly or in combination to maintain sample compartment constant at any temperature between 0 and 100°C. The standard Model DU cell compartment can be held to less than one degree change for a ten degree change in ambient temperature.

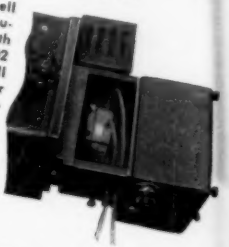


***Designed for*** greatest measurement accuracy with the Model DU . . . and for special measurements such as chemical analyses at constant temperature; the study of reaction rates at various temperatures; precise measurement of extinction values, and other applications where close temperature control is essential.

## SHORT PATH FLOW CELL

### For extremely short path length measurements on flowing or static samples

Consists of two flat, transparent plates which form an internal cell through which sample can be circulated without exposure to air. Path lengths from 0.05 to 2.5 mm (0.002 to 0.098 in.) available. A special cell compartment containing cell holder and precision positioning carriage attaches directly to Model DU.



Quartz optics permit full-range measurements, 220 to 1000 mmu . . . All critical surfaces optically polished to ¼ wavelength for precise measurements . . . Extreme flatness of plates allows fluid-tight seal without gaskets or sealing compounds.

***Designed for*** flowing or static measurements on strongly absorbing samples without dilution; on blood samples in vivo under anaerobic conditions (such as determining oxygen capacities of whole blood); for microchemical studies of reaction rates, etc.

## 50 cm. LIQUID ABSORPTION CELL

### For long path length measurements on weakly absorbing samples

To conserve sample volume, the cell is only 25 cm. long, the light beam passing twice through the sample before reaching the phototube.

A special lightproof cell compartment provides a convenient means of standardization without the necessity of using a reference cell. All optical parts are of quartz to utilize full Model DU measurement range. Liquid seals made without gaskets to avoid sample contamination. Careful design eliminates scattered light effects.

***Designed for*** dilute solutions and weakly absorbing samples where a long path length is required. Also for use with flowing samples and for utmost sensitivity in nephelometric measurements to determine, in addition to intensity, the distribution and average size of light-scattering particles.

# IDEAL ADSORBENTS

## FOR THE BIOLOGICAL INDUSTRY BY Filtrol

### PROPERTIES:

| | SUPER FILTROL* | FILTROL* X-202 | FILTROL* THIAMIN GRADE |
|---|---|---|---|
| USE: | GENERAL ADSORBENT FOR ANTI-BIOTICS AND VITAMINS | CHROMATO-GRAPHIC ADSORBENT FOR VITAMINS | GENERAL ADSORBENT FOR THIAMIN |
| PHYSICAL STATE: | Powder | Powder | Powder |
| COLOR: | Light Grey | White | Light Grey |
| ODOR: | Odorless | Odorless | Odorless |
| KEEPING QUALITIES: | Stable | Stable | Stable |
| WEIGHT PER CU. FT. (LBS.) | 45 | 45 | 45 |
| SURFACE AREA (SQ. M. PER GR.**) | 300 | 300 | 300 |
| FREE MOISTURE | 13.0-16.0 % | 13.0-16.0% | 13.0-16.0% |
| pH (approx.)*** | 3 | 3 | 3 |
| MESH: (T-200) % | 93-95 | 84-96 | 93-95 |

** Approx. after 850° F Calcination as determined by Nitrogen.
***Of SLURRY

### FILTROL ADSORBENTS

Filtrol activated adsorbents are gaining wide popularity in the manufacture and estimation of anti-biotics, vitamins, and other biological products. These adsorbents are pure, highly-refined powders prepared from selected Bentonite clays by perfected Filtrol methods of chemical activation. Filtrol adsorbents possess selective adsorptive capacity for a number of the vitamins and anti-biotics and they are carefully standardized to perfect uniformity during manufacture.

### FILTROL DESICCANTS

Special small size packets of Desiccite #25 are now being widely supplied to pharmaceutical houses for individually bottled preparations such as vitamins and plasmas.

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escribir pidiendo el nombre del agente en su pas

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Please send us a sample of:
☐ Super Filtrol ☐ Filtrol X-202 ☐ Filtrol Thiamin Grade

FIRM NAME_____

ATTENTION_____

STREET_____

CITY_____ ZONE_____ STATE_____

☐ We are interested in securing more information about Desiccite #25 . . . the profitable method of eliminating losses of potency and quality due to moisture.